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SIGNIFICANCE OF THE ALBUMIN-GLOBULIN RATIO OF SERUM

DANIEL MELNICK, PH.D.*

HENRY FIELD JR., M.D.

AND

CHRISTOPHER G. PARNALL JR., M.D.†

ANN ARBOR, MICH.

On the basis of solubility measurements, Sørensen [1] postulated that certain soluble proteins, including serum albumin and serum globulin, are not chemical entities but exist as a system of reversibly dissociable components held together by secondary valence forces. Recent investigations, following this lead, have thrown much doubt on the significance of the albumin-globulin ratio as employed in clinical practice. Ultracentrifugal studies [2] have indicated that a sensitive equilibrium exists between the molecular species constituting the serum protein complex. Thus, the ratio of small molecules to large molecules in a single sample of serum can be changed by aging, by simple dilution with water or Ringer's solution [2a] and even by the presence of other protein molecules in the solution.[2b] Although normal native serum appears to contain three molecular species and additional dispersion states are evident in pathologic serums, these in no way correspond with the albumin and globulin fractions obtained by "salting out." [3] A marked interaction between the component proteins appears to take place readily, so that slight environmental changes cause large variations in the proportion

* Upjohn Fellow in Clinical Research, 1937-1940.

† Upjohn Fellow in Clinical Research, 1937-1938.

From the Department of Internal Medicine, Medical School, University of Michigan.

1. Sørensen, S. P. L.: The Constitution of Soluble Proteins, Compt. rend. d. trav. du lab. Carlsberg **18**:1, 1930.

2. (*a*) von Mutzenbecher, P.: Dissoziationen und Assoziationen der Serummoleküle, Biochem. Ztschr. **266**:259, 1933. (*b*) Pedersen, K. O.: Ultracentrifugal Studies on Protein Mixtures, Compt. rend. d. trav. du lab. Carlsberg, série physiol. **22**:427, 1938. (*c*) McFarlane, A. S.: An Ultracentrifugal Investigation of the Serum Proteins, Biochem. J. **29**:407 (Feb.) 1935; (*d*) The Ultracentrifugal Protein Sedimentation Diagram of Normal Human, Cow and Horse Serum, ibid. **29**:660 (March) 1935; (*e*) The Behavior of Pathological Sera in the Ultracentrifuge, ibid. **29**:1175 (May) 1935.

3. McFarlane (footnote 2 *c*, *d* and *e*).

of one species to another. Measurements of the migration of serum protein molecules in an electric field (electrophoresis) have also demonstrated [4] that preparations obtained by the customary salting-out procedures are not homogeneous but contain other fractions which can be isolated in the chambers of the apparatus. Observations of maximal, rather than final, colloid osmotic pressure values for samples of serum [5] are in accordance with the total protein content but not with the albumin-globulin ratio. Agreement was obtained with the values predictable from the amounts of the two protein fractions present only after measurement of the "equilibrium" oncotic pressure after twenty-four hours. However, it was possible to obtain osmotic pressure curves with normal serums indistinguishable from those of hypoproteinemic serums over the entire twenty-four hour period by simple dilution of the former with saline solution. The reverse was also obtained experimentally. Chemical evidence supporting the view that the salted-out albumin and globulin fractions are artefacts has been obtained from amino acid analyses of such fractions.[6] The fractionation of serum by increasing concentrations of neutral salts yielded albumins and globulins of differing basic amino acid composition. However, despite variations in the ratio of these two fractions in a number of serums, the basic amino acid composition of the total coagulable protein in each case was found to be constant.

These studies have led to the "orosin" hypothesis,[7] which postulates that the serum protein complex is composed of two or more unstable coprecipitation systems in mutual equilibrium. Variations in concentration of the isolated protein fractions i. e., in the albumin-globulin ratio, are believed to result from environmental disturbances in the normal balance between the component systems before the electrolytes were introduced.

In the present study this hypothesis was investigated experimentally. Normal and hypoproteinemic serums were exposed simultaneously to the influence of the same environmental conditions by dialysis of one against the other for variable periods prior to addition of the salting-out reagent. In this way it was believed possible to determine the influence of variations in environmental conditions on the albumin-globulin ratios previously found to be characteristic of such serums.

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4. Tiselius, A.: Electrophoresis of Serum Globulin: II. Electrophoretic Analysis of Normal and Immune Serum, Biochem. J. **31**:1464 (Sept.) 1937.

5. Yanagi, K.: A Clinical and Experimental Study of the Stability of Colloid Osmotic Pressure of Serum Protein, J. Clin. Investigation **14**:853 (Nov.) 1935.

6. Block, R. J.: The Basic Amino Acids of Serum Proteins, J. Biol. Chem. **103**:261 (Nov.) 1933.

7. Block, R. J.: Proteins of the Nervous System Considered in the Light of the Prevailing Hypotheses on Protein Structure, Yale J. Biol. & Med. **9**:445 (May) 1937.

EXPERIMENTAL METHOD AND RESULTS

Howe's method,[8] employing a 1:2 solution of potassium dihydrogen phosphate (KH_2PO_4) and potassium phosphate (K_2HPO_4) to precipitate the globulin, was used throughout this study. This procedure gives essentially the same results as the sodium sulfate (Na_2SO_4) salting-out method but is more reproducible from day to day.[9]

Influence of Simple Dilution and Incubation on the Salting-Out Properties of the Serum Protein Complex.—Serums from 3 normal persons were diluted with an equal volume of 0.9 per cent saline solution and immersed in a water bath at 37 C. for twenty-four hours. A few small crystals of thymol were added as a preservative.[10] The results, summarized in table 1, indicate that dilution of the normal concentration of serum protein to the hypoproteinemic level and subsequent incubation at body temperature do not cause a decrease in the albumin-globulin ratio, characteristic of hypoproteinemic serums.

TABLE 1.—*Stability of the Albumin-Globulin Ratio of Normal Serums Diluted with an Equal Volume of Physiologic Solution of Sodium Chloride and Maintained at 37 C. for Twenty-Four Hours*

Sample	Serum	Protein Concentration*			
		Total, per Cent	Albumin, per Cent	Globulin, per Cent	Albumin-Globulin Ratio
A	Control; undiluted	6.37	4.81	1.56	3.08
	Experimental	3.19†	2.36	0.83	2.85
R	Control; undiluted	7.90	5.40	2.50	2.16
	Experimental	3.95†	2.68	1.27	2.10
L	Control; undiluted	7.54	4.99	2.55	1.96
	Experimental	3.77†	2.52	1.25	2.01

* In the calculation of the protein concentration in these normal serums the value for nonprotein nitrogen was considered to be 35 mg. per hundred cubic centimeters.
† Calculated values.

Dialysis of Normal Versus Hypoproteinemic Serums.—For the dialysis experiments several units of the apparatus sketched in the accompanying diagram were used. The diagram is self explanatory. Cellophane was used as the semipermeable membrane.[11] Markedly hypoproteinemic serums with low albumin-globulin ratios

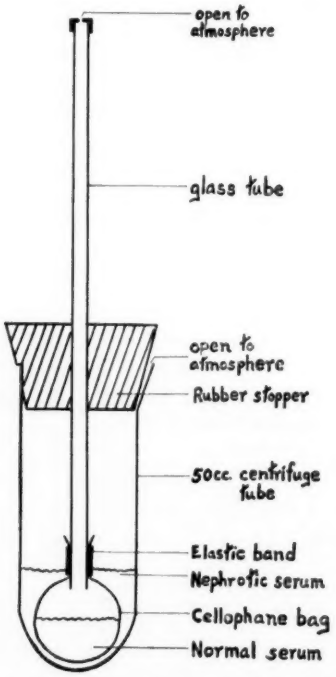
8. Howe, P. E.: The Relative Precipitating Capacity of Certain Salts When Applied to Blood Serum or Plasma and the Influence of the Cation in the Precipitation of Proteins, J. Biol. Chem. **57**:241 (Aug.) 1923.

9. The salting out of the globulin fraction from each sample of serum was carried out in duplicate. The average deviation of a single albumin determination from the average value obtained with each sample tested was ± 1.0 per cent, with a maximal deviation of ± 2.0 per cent. Total nitrogen minus nonprotein nitrogen was multiplied by 6.25 to obtain the value for protein.

10. Control determinations have indicated that this preservative exerts no effect on the salting-out properties of the serum protein complex.

11. Cellophane no. 300, furnished by E. I. du Pont de Nemours and Company, Wilmington, was used. It is impermeable to protein (Lavietes, P. H.: Anaerobic Ultrafiltration, J. Biol. Chem. **120**:267 [Aug.] 1937. Yanagi[5]).

were obtained from patients in the nephrotic stage of glomerulotubular nephritis. By dialyzing such serum against normal serum it is possible to subject the serum protein complex in each sample to the same environmental influences. Water will leave the hypoproteinemic serum to dilute the normal sample. The temperature of both of the serums and, at equilibrium, the protein concentration, p_H and concentration of the plasma crystalloids will be the same. The serum proteins, however cannot pass from one compartment to the other. If the "orosin" hypothesis [7] is correct, the ratios of albumin to globulin on each side of the cellophane membrane should change from the original values and tend to approximate each other.



Unit used for the dialysis of normal against nephrotic serum.

A typical series of experiments is described. Confirmatory results were derived from tests with normal and nephrotic serums obtained from other persons.

The dialysis experiments were conducted at first at 4 C. in order to minimize bacterial contamination. The serums were collected and the experiments set up with aseptic precautions. Because of the low temperature of incubation no thymol was added as preservative. The results of these tests are presented in table 2. In both control serums, nephrotic and normal, incubated under the same conditions, there were no changes in the salting-out behavior of the serum protein complex. As a result of the dialysis the protein concentrations in both serums approached each other, the other environmental factors likewise tending to equilibrate them-

selves on each side of the membrane. However, the albumin-globulin ratios did not change.

The lack of appreciable change in the albumin-globulin ratio might have been due to inhibition of the association and dissociation of the serum protein molecules by the low temperature of incubation. Accordingly aliquots of the same samples of serum previously dialyzed one against the other were maintained at 56 C. for a three hour period. At this temperature the possibility of bacterial contamination is negligible; therefore no preservative was used. If the molecular changes in the serum protein molecules are chemical, the elevated temperature may be expected to promote such changes more readily. Indeed, incubation of serum at 56 C. has been reported[12] to cause a transformation of serum albumin into serum globulin. Table 3 gives the results of these tests.

A definite change in the salting-out properties of the serum protein complex was observed. In all cases the albumin-globulin ratios were markedly less than the initial values (table 2). These results, however, do not indicate any change of

TABLE 2.—*Stability of the Albumin-Globulin Ratio of Normal and Nephrotic Serums Maintained at 4 C. and Dialyzed One Against the Other*

Serum	Protein Concentration*			
	Total, per Cent	Albumin, per Cent	Globulin, per Cent	Albumin-Globulin Ratio
Normal (immediate analyses)	7.42	5.06	2.36	2.14
48 hours at 4 C. (control, without dialysis)	7.22	4.90	2.32	2.12
120 hours at 4 C. (control, without dialysis)	7.30	4.93	2.37	2.08
Nephrotic (immediate analyses)	3.21	0.86	2.35	0.37
48 hours at 4 C. (control, without dialysis)	3.15	0.76	2.39	0.32
120 hours at 4 C. (control, without dialysis)	3.17	0.92	2.25	0.41
Normal (3 cc.) dialyzed against nephrotic (7 cc.)				
Normal 48 hours at 4 C. (4.6 cc.)	4.79	3.42	1.37	2.50
120 hours at 4 C. (4.7 cc.)	4.63	3.08	1.55	1.99
Nephrotic 48 hours at 4 C. (5.7 cc.)	3.55	0.85	2.70	0.32
120 hours at 4 C. (5.6 cc.)	4.06	1.10	2.96	0.37

* The value for nonprotein nitrogen was considered to be 35 mg. per hundred cubic centimeters in each case.

albumin to globulin. If this transformation were possible, the ratio of the fractions in the dialyzed sample of normal serum in which environmental factors may have been expected to favor such a change should have been much less than that in the control. This was not the case. Furthermore, the dialyzed sample of nephrotic serum, in a position presumably favoring an increase in the albumin-globulin ratio, likewise showed a decrease in this ratio. The changes observed in these serums are attributed to incipient denaturation of the serum proteins. The globulin fraction is salted out in either case, but in the second instance, in addition, the partially denatured albumin fraction is also precipitated. That denaturation can occur without precipitation is indicated from analyses of four normal serums; the results are summarized in table 4. In these tests the only change observed

12. Moll, L.: Ueber kunstliche Umwandlung von Albumin in Globulin, Beitr. z. chem. Physiol. u. Path. **4**:563 (Nov.) 1903. Rusznyak, S.: Physikalisch-chemische Untersuchungen an Körperflüssigkeiten: VII. Die Umwandlung von Albumin in Globulin, Biochem. Ztschr. **140**:179, 1923. Desbordes, J.: Notion d'exsudat et de transsudat dans les liquides d'épanchement: Signification du rapport sérine/globuline, Compt. rend. Soc. de biol. **127**:784, 1938.

during the heating of the samples of diluted serum at 100 C. was the appearance of a slight opalescence. The normal p_H of serum is sufficiently removed from the isoelectric point of the proteins so that heat coagulation does not occur. Despite the fact that no visible precipitate formed, all the serum albumin was denatured and was salted out with the globulin fraction. Incipient denaturation of serum albumin comparable to that described in the present report may be the factor primarily responsible for the alleged conversion of albumin to globulin which has been reported in many papers.[13]

TABLE 3.—*Effect of Heating on the Albumin-Globulin Ratio of Normal and Nephrotic Serums Previously Maintained at 4 C. and Dialyzed One Against the Other*

Serum	Protein Concentration*			
	Total, per Cent	Albumin, per Cent	Globulin, per Cent	Albumin-Globulin Ratio
Normal: 140 hours at 4 C., then heated 3 hours at 56 C. (control without dialysis)	7.22	3.28	3.94	0.83
Nephrotic: treated as above (control without dialysis)	3.13	0.36	2.77	0.13
Normal (3 cc.) dialyzed against nephrotic (7 cc.) 140 hours at 4 C., then heated 3 hours at 56 C.				
Normal (4.7 cc.)	4.48	2.32	2.16	1.08
Nephrotic (5.6 cc.)	4.07	0.51	3.56	0.14

* The value for nonprotein nitrogen was considered to be 35 mg. per hundred cubic centimeters in each case.

TABLE 4.—*Albumin-Globulin Ratio of Serum Diluted with Physiologic Solution of Sodium Chloride (1:10) and Heated at 100 C. for Five Minutes*

Serum Sample	Initial Protein Concentration*			Albumin-Globulin Ratio	Albumin Concentration after Heat Treatment	
	Total, per Cent	Albumin, per Cent	Globulin, per Cent		Kjeldahl Determination, per Cent	Result of Protein Test†
A	6.37	4.81	1.56	3.08	0.0	Negative
B	7.90	5.40	2.50	2.16	0.0	Negative
M	7.56	4.87	2.69	1.81	....	Negative
P	7.42	5.06	2.36	2.14	....	Negative

* The value for nonprotein nitrogen was considered to be 35 mg. per hundred cubic centimeters in each case.

† Sulfosalicylic acid (20% solution) was added to the filtrate after the salting out of the globulin fraction.

13. (*a*) Herzfeld, E., and Klinger, R.: Studien zur Chemie der Eiweisskörper: I. Die Eiweissfraction des Blutplasmas; II. Zur Theorie der Bakterien-Agglutination, Biochem. Ztschr. **83**:228, 1917. (*b*) Fischer, A.: Antiprothrombin und Globuline, ibid. **244**:464, 1932. (*c*) Wu, H.: Effect of Removal of Lipoid on Precipitability of Serum Proteins by Neutral Salts, Chinese J. Physiol. **7**:125 (July) 1933. (*d*) Kozawa, S.; Iwatsuru, R., and Adachi, T.: Studien über Harneiweiss, Biochem. Ztschr. **260**:313, 1933. (*e*) Hadáček, J.: Albumins and Globulins in Blood Serum, Časop. lék. česk. **17**:96, 1937; abstracted, Chem. Abstr. **31**:5823 (Aug.) 1937. (*f*) Footnote 12.

Tests were carried out with aliquots of the same serums but with the dialysis continued at body temperature. A few small crystals of thymol were added as a preservative. The results are presented in table 5. In this experiment true equilibrium was attained, the concentrations of protein on both sides of the membrane being equal. Despite this the albumin-globulin ratios of both serums were the same as those of the controls without dialysis. Denaturation of the proteins in these tests was negligible. In the confirmatory tests with normal and nephrotic serums obtained from other persons the dialysis was allowed to proceed for forty hours at 37 C. throughout. No evidence of protein denaturation was observed in these serums.

Influence of Serum Lipids on the Salting-Out Behavior of Serum Proteins.—The serum lipids do not dialyze through the cellophane membrane.[14] However, the addition of these lipids to serum to yield clear solutions does not affect the precipitation limits of the proteins.[15] In the present study the serum lipids from nephrotic serums were isolated[16] and added to physiologic solution of sodium

TABLE 5.—*Effect of Body Temperature on the Albumin-Globulin Ratio of Normal and Nephrotic Serums Maintained Previously at 4 C. and Dialyzed One Against the Other*

Serum	Protein Concentration*			
	Total, per Cent	Albumin, per Cent	Globulin, per Cent	Albumin-Globulin Ratio
Normal: 155 hours at 4 C., then heated 15 hours at 37 C. (control without dialysis)	7.16	4.64	2.52	1.84
Nephrotic: treated as above (control without dialysis)	3.17	0.59	2.58	0.23
Normal (3 cc.) dialyzed against nephrotic (7 cc.) 155 hours at 4 C. and then 15 hours at 37 C.				
Normal (5.4 cc.)	4.33	2.88	1.45	1.99
Nephrotic (4.9 cc.)	4.36	0.85	3.51	0.24

* The value for nonprotein nitrogen was considered to be 35 mg. per hundred cubic centimeters in each case.

chloride. The suspension was then used to dilute normal serums (1:2), and the "solution" was incubated at body temperature for forty hours. No change in the albumin-globulin ratio was found.

Influence of Urinary Constituents On the Salting-Out Behavior of Serum Proteins.—From the basic amino acid analysis of urinary protein, Block and his associates[17] have concluded that urinary protein is not nearly all albumin but is total serum protein. Determinations conducted by Kozawa and his associates[13d] with freshly voided urinary protein gave an albumin-globulin ratio of approximately 5:1. A repetition of these tests on the same samples of urine after dialysis and

14. Lavietes, P. H.: Anaerobic Ultrafiltration, J. Biol. Chem. **120**:267 (Aug.) 1937.

15. Theorell, H.: Studien über die Plasmalipoide des Blutes, Biochem. Ztschr. **223**:1, 1930.

16. Sørensen,[1] Wu.[13e]

17. Block, R. J.; Darrow, D. C., and Cary, M. K.: The Basic Amino Acids of Serum Proteins: III. A Chemical Relationship Between Serum Proteins of Various Origins, J. Biol. Chem. **104**:347 (Feb.) 1934.

concentration to simulate conditions in the serum yielded values approximating 1 : 1. These were identical with the ratios obtained with serums from the same patients. These experiments have led to the conclusion that urinary protein is total serum protein but that because of the influence of the environmental factors, including the well known solvent action of urea solutions for protein, it is salted out like serum albumin. However, in these tests ample opportunities for incipient denaturation of the urinary protein during dialysis and concentration were present, so that the decrease noted in the albumin-globulin ratio may have been due entirely to such a factor. If urinary constituents modify the salting-out behavior of the protein excreted, the addition of serum to urine should result in an increase in the albumin-globulin ratio, giving one characteristic of urinary proteins.

One cubic centimeter samples of normal and nephrotic serums were added to 9 cc. samples of urine collected from these persons. The serums and urines were also crossed so that normal serums in pathologic urine were obtained, and vice versa. After a twenty-four hour incubation period at 37 C. the samples were tested to determine whether any change occurred as compared with the initial albumin-globulin ratios of the serums.

In these tests the globulin fraction was estimated nephelometrically rather than by the conventional Kjeldahl nitrogen determination. The level of nonprotein nitrogen in the urine filtrate, subsequent to salting out, is relatively high in relation to that of albumin nitrogen, so that a small error in the determination can markedly alter the value obtained for the protein. The turbidity obtained when the salting-out reagent was added to the sample of serum diluted with urine and subsequently incubated was compared immediately with that obtained with the same serums diluted with saline solution. The readings were made before flocculation of the globulin particles occurred. This method has been tested for reproducibility and with varying quantities of serum; the results are believed to be accurate to within ± 10 per cent.[18] Such a degree of accuracy is satisfactory for the purpose of this investigation. In all cases the turbidities due to the globulin fraction, salted out after the period of incubation, were the same regardless of whether saline solution or urine was used as the diluent. No evidence of denaturation of the serum proteins, judging from their salting-out behavior, was noted in the control tests. These experiments seem to indicate that urinary protein is not total serum protein but is derived principally from the albumin fraction.

COMMENT

The constancy of the albumin-globulin ratio in the present studies does not support the "orosin" hypothesis.[7] Normal and hypoproteinemic serums when subjected to the same environmental influences still give the same initial albumin-globulin ratios characteristic of such serums. These findings do not indicate that native serum contains discrete proteins identical with those salted out. It is our opinion that the dissociation and association reactions of the serum protein complex, which are responsible for the sensitive equilibrium between the molecular species in native serum, must occur within independent systems. On the addition of the salting-out reagent the components in each of these

18. A method based on the same principle but using a different salting-out reagent has recently been described (Paic, M. M., and Deutsch, V.: Microdosage colorimétrique des globulines, Bull. Soc. chim. biol. **20**:1112 [Sept.-Oct.] 1938).

systems combine, probably by means of residual valencies, into a product that is insoluble under the imposed conditions. Likewise, it should be emphasized that the ultracentrifugal technic measures simply the number of dispersion states in which the serum protein complex exists and the relative concentrations associated with them. The chemical identities of the molecular species are not determined.

When serum is diluted with physiologic solution of sodium chloride, there is a marked fall of specific osmotic pressure of the serum protein as estimated from the stable readings taken after twenty-four hours or longer.[19] This effect has been shown in the present study not to be due to any change of albumin to globulin. It has been attributed by Peters and Van Slyke [20] to the appreciable volume of the proteins. However, measurements [21] of the specific apparent volume of serum albumin and serum globulin in aqueous solution and in plasma do not seem to support such an explanation. The most plausible explanation is derived from ultracentrifugal studies [2c] of artificial mixtures of the molecular species in native serum; the proteins of smaller molecular size on dilution associate to form larger molecules, and, since osmotic pressure varies inversely with the molecular weight, there is accordingly a decrease in the specific oncotic pressure of serum protein. This disproportion between the oncotic pressure and the protein concentration, however, is not manifest in the values for maximal colloid osmotic pressure obtained at the end of the sixth to the seventh hour.[5] This is strongly suggestive that some change in the serum protein complex (association into the larger molecular species) occurs several hours after the serum is placed in the osmometer. Thus, colloid osmotic pressure measurements in vitro may not represent the true state of affairs as they exist in the plasma.

As the albumin-globulin ratio, determined by salting-out procedures, does not reflect the dispersion state of the serum protein or the relative amounts of the molecular species in any given serum,

19. Verney, E. B.: The Osmotic Pressure of the Proteins of Human Serum and Plasma, J. Physiol. **61**:319 (June) 1926. Fishberg, E. H.: The Relations of the Serum Proteins and Lipids to the Osmotic Pressure, J. Biol. Chem. **81**:205 (Jan.) 1929. Kylin, E.: Studien über den kolloid-osmotischen (onkotischen) Druck, Ztschr. f. d. ges. exper. Med. **93**:480 (April) 1934. Grönwall, A.: Ueber die Bedeutung des Verhältnisses zwischen Bluteiweisskonzentration und dem sogenannten kolloidosmotischen Druck, Biochem. Ztschr. **276**:223, 1935. Yanagi.[5]

20. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: I. Interpretations, Baltimore, Williams & Wilkins Company, 1932.

21. Svedberg, T., and Sjögren, B.: The Molecular Weights of Serum Albumin and of Serum Globulin, J. Am. Chem. Soc. **50**:3318 (Dec.) 1928. Oberst, F. W.: Specific Volume of Plasma and Serum Proteins in Pregnant and in Parturient Women and Their Newborn Children as Derived from Viscosity Measurements, J. Clin. Investigation **18**:799 (Nov.) 1939.

determinations of the ratio seem to have little value in predicting the true oncotic pressure in vivo. Furthermore, to attribute to the albumin fraction (estimated by salting out) major importance in preventing the passage of the fluids of plasma across the wall of the capillary into the tissues does not seem valid in the light of the recent physicochemical studies of the serum protein complex.

It is probable that changes in the serum protein dispersion state may occur in vivo comparable to those observed in the ultracentrifuge, with corresponding changes in oncotic pressure but not in the albumin-globulin ratios. In dogs subjected to prolonged plasmapheresis (experimental plasma depletion) there is a reduction in the serum protein concentration, with a corresponding decrease in the albumin-globulin ratio.[22] In comparable experiments [23] it was found that the parallelism between change in plasma volume and change in serum protein concentration could be disturbed by a significant decrease in the volume of red cells. Under such circumstances the plasma volume may actually be greater than the initial normal value despite the hypoproteinemia and the decreased albumin-globulin ratio. An alteration in the serum protein dispersion state resulting in an increase in the smaller molecular species can account for this. The reverse may also take place in vivo. Dogs subjected to prolonged plasmapheresis will become edematous much more easily when large quantities of saline solution are given orally or parenterally.[24] However, despite the formation of edema by such an experimental procedure, neither the total serum protein concentration nor the albumin-globulin ratio is markedly affected when compared with the values for the same dog during the preceding hypoproteinemia without edema.[25] The animals, except for hypoproteinemia,

22. McNaught, J. B.; Scott, V. C.; Woods, F. M., and Whipple, G. H.: Blood Plasma Protein Regeneration Controlled by Diet: Effects of Plant Proteins Compared with Animal Proteins; the Influence of Fasting and Infection, J. Exper. Med. **63**:277 (Feb.) 1936.

23. Melnick, D., and Cowgill, G. R.: The Serum Protein Complex as a Factor in Regulating Blood Volume, Proc. Soc. Exper. Biol. & Med. **35**:312 (Nov.) 1936.

24. (*a*) Leiter, L.: Experimental Nephrotic Edema, Arch. Int. Med. **48**:1 (July) 1931. (*b*) Barker, M. H., and Kirk, E. J.: Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, ibid. **45**:319 (March) 1930. (*c*) Darrow, D. C.; Hopper, E. B., and Cary, M. K.: Plasmapheresis Edema: I. The Relation of Reduction of Serum Proteins to Edema and the Pathological Anatomy Accompanying Plasmapheresis, J. Clin. Investigation **11**:683 (July) 1932.

25. (*a*) Shelburne, S. A., and Egloff, W. C.: Experimental Edema, Arch. Int. Med. **48**:51 (July) 1931. (*b*) Lepore, M. J.: Experimental Edema Produced by Plasma Protein Depletion, ibid. **50**:488 (Sept.) 1932. (*c*) Kirk, E. J.: Studies of Edema, Especially the Edema of Renal Origin, Am. J. Clin. Path. **5**:21 (Jan.) 1935. Barker and Kirk.[24b] Darrow and others.[24c]

are normal and show no evidence of vascular permeability to protein or changes in blood pressure.[24a] The capillaries are permeable to salt solution in both directions, and the animals, as in most cases of edema in the human being, have no difficulty in excreting salts.[25b] Possibly in such conditions of hypoproteinemia with excessive intake of sodium chloride a decrease in the amount of the smaller molecular species in serum with a corresponding increase in the larger molecular forms occurs; a drop in the oncotic pressure in vivo would follow.

Although the albumin globulin ratios as determined by salting-out procedures may not be indicators of the oncotic pressure in vivo, such ratios are not necessarily without significance. The fact that they are altered in certain pathologic states and remain constant under the experimental conditions described here would seem to indicate that the ratios obtained are real and indicative of the relative amounts of these two independent protein systems in native serum. Association and dissociation changes must occur within these independent systems.

SUMMARY

The albumin-globulin ratios characteristic of normal and hypoproteinemic serums represent the relative amounts of two independent protein systems, which may be separated by salting-out procedures. Dissociation and association phenomena attributed to the serum protein molecules must occur within these independent systems. Exposing normal and hypoproteinemic serums to the same environmental factors by dialysis of one against the other does not alter the ratio of one protein fraction to another. The influence of incipient denaturation on the salting-out behavior of the serum protein complex has been studied and serves to explain the alleged conversion of albumin to globulin reported by others. Urinary protein does not represent total serum but is derived principally from the albumin fraction.

The inadequacy of colloid osmotic pressure measurements in vitro and of the determinations of albumin and globulin for predicting the true oncotic pressure in vivo are discussed in the light of recent physicochemical studies of the serum protein complex.

A PRACTICAL METHOD FOR THE MEASUREMENT OF GLOMERULAR FILTRATION RATE (INULIN CLEARANCE)

WITH AN EVALUATION OF THE CLINICAL SIGNIFICANCE OF THIS DETERMINATION

ALF S. ALVING, M.D.
AND
BENJAMIN F. MILLER, CH.E., M.D.
CHICAGO

The kidney, by virtue of its peculiar structure, lends itself particularly well to quantitative measurements. Until recently most studies concerning the quantitative aspects of renal function have dealt with the excretion of urea and exogenous creatinine. The extensive studies of Ambard,[1] Addis,[2] and Möller, McIntosh and Van Slyke[3] have developed the laws governing the excretion of urea by the normal and the diseased human kidney. These studies have led to practical tests of renal function. Of these, the Ambard coefficient is now of historical interest only. The Addis urea ratio, though somewhat too complicated for routine use, is a good quantitative test of renal function. The urea clearance test of Van Slyke and his associates has been adopted universally as a simple and precise estimate of the functional state of the kidneys. Recent studies[4] have shown that the excretion of urea depends on a balance between the glomerular filtration rate and tubular reabsorption.

From the Department of Medicine, University of Chicago.

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4. (*a*) Van Slyke, D. D.; Hiller, A., and Miller, B.: The Clearance, Extraction Percentage and Estimated Filtration of Sodium Ferrocyanide in the Mam-

(Footnote continued on next page)

During the past decade there has been a great advance in knowledge of the excretion characteristics of the human kidney, in large part due to the studies of Smith and Shannon and their associates.[5] It is now possible to make precise measurements of the glomerular filtration rate, the effective renal blood flow and the capacity of the tubular cells to reabsorb or excrete certain compounds. Many of these measurements are too difficult at present for clinical purposes, but, as will be shown in this paper, one can measure the glomerular filtration rate rather simply with both normal and diseased persons by employing a simplified inulin clearance test.

Inulin, a polysaccharide which is not metabolized by the body, has the unique distinction of being excreted consistently by glomerular filtration in the human kidney without tubular excretion or reabsorption.[6] If one considers the formula for the clearance, UV/B (U being the concentration of the excreted compound in the urine, B its concentration in the blood [or plasma] and V the flow of urine in cubic centimeters per minute), it can be seen that for such a compound as inulin the clearance is equal to the glomerular filtration rate. In other words, the milligrams of inulin found per minute in the vesical urine are contained in that volume of plasma "cleared" per minute. Since inulin is excreted only by filtration, the volume (in cubic centimeters) of plasma

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5. (*a*) Smith, H. W.: The Physiology of the Kidney, New York, Oxford University Press, 1937; Kidney, Ann. Rev. Physiol. **1**:503, 1939; Studies in the Physiology of the Kidney, Publication of the University Extension Division, University of Kansas, Lawrence, Kan., 1939. (*b*) Shannon, J. A.: Renal Tubular Excretion, Physiol. Rev. **19**:63 (Jan.) 1939; (*c*) The Renal Excretion of Creatinine in Man, J. Clin Investigation **14**:403 (July) 1935. (*d*) Smith, H. W.; Goldring, W., and Chassis, H.: The Measurement of the Tubular Excretory Mass, Effective Renal Blood Flow and Filtration Rate in the Normal Human Kidney, ibid. **17**:263 (May) 1938. (*e*) Shannon, J. A., and Fisher, S.: The Renal Tubular Reabsorption of Glucose in the Normal Dog, Am. J. Physiol. **122**:765 (June) 1938. (*f*) Smith, H. W.; Goldring, W.; Chassis, H., and Ranges, H. A.: Observations on the Effective Renal Blood Flow and the Functional Excretory Mass in Man, with Special Reference to Essential Hypertension, ibid. **123**:189 (July) 1938.

6. Recent preliminary studies by Smith suggest that mannitol and solitol are excreted entirely by glomerular filtration (Smith, H. W.: Studies in the Physiology of the Kidney, Publication of the University Extension Division, University of Kansas, Lawrence, Kan., 1939).

cleared must be equal to the volume of filtrate formed in the glomeruli per minute. This follows from the fact that inulin, being freely filtrable at the glomerulus, has essentially the same concentration in the protein-free glomerular filtrate as in the plasma.

The evidence that inulin clearance is an exact measure of glomerular filtration in the normal human being has been extensively reviewed by Smith.[5a] Experiments recently performed by Miller, Alving and Rubin [7] support the results of others for normal persons and add evidence for nephritic and hypertensive persons.

The clearances of other compounds than inulin have been proposed for clinical measurement of the glomerular filtration rate. Rehberg,[8] the first investigator to attempt such measurements, employed the clearance of exogenous creatinine. That exogenous creatinine is excreted by the tubules as well as the glomeruli in man has been demonstrated clearly by Shannon.[5e] Therefore it is apparent that the Rehberg clearance test should be abandoned as a clinical measure of the glomerular filtration rate. The situation with endogenous creatinine is more complex. Experiments with this compound [9] indicate that endogenous creatinine may be excreted at the level of the filtration rate, but that in many normal and in most nephritic subjects the endogenous creatinine clearance is considerably higher than the inulin clearance. Despite these experiments, which were performed with a specific, enzymatic method for creatinine (Miller and Dubos [10]), several investigators [11] have advocated the endogenous creatinine clearance, as determined by nonspecific analytic methods, for clinical measurement of the glomerular filtration

7. Miller, B. F.; Alving, A. S., and Rubin, J.: The Renal Excretion of Inulin at Low Plasma Concentrations of This Compound, and Its Relationship to the Glomerular Filtration Rate in Normal, Nephritic and Hypertensive Individuals, J. Clin. Investigation **19**:89 (Jan.) 1940.

8. Rehberg, P. B.: Studies on Kidney Function: I. The Rate of Filtration and Reabsorption in the Human Kidney, Biochem. J. **20**:447 (April) 1926.

9. (*a*) Miller, B. F., and Winkler, A.: Renal Excretion of Endogenous Creatinine in Man: Comparison with Exogenous Creatinine and Inulin, J. Clin. Investigation **17**:31 (Jan.) 1938. (*b*) Miller, B. F.; Alving, A. S.; Allinson, M. J. C., and Flox, J.: Experiments, to be published.

10. Miller, B. F., and Dubos, R.: Determination by a Specific, Enzymatic Method of the Creatinine Content of the Blood and Urine from Normal and Nephritic Individuals, J. Biol. Chem. **121**:457 (Nov.) 1937.

11. (*a*) Popper, H., and Mandel, E.: Filtrations- und Resorptionsleistung in der Nierenpathologie, Ergebn. d. inn. Med. u. Kinderh. **53**:685, 1937. (*b*) Steinitz, K., and Türkand, H.: The Determination of the Glomerular Filtration by the Endogenous Creatinine Clearance, J. Clin. Investigation **19**:285 (March) 1940. (*c*) Arkin, A., and Popper, H.: Urea Reabsorption and Relation Between Creatinine and Urea Clearance in Renal Disease, Arch. Int. Med. **65**:627 (March) 1940.

rate in diseased as well as in normal kidneys. Until more is known of the excretion characteristics of endogenous creatinine it seems best not to employ this clearance as a measure of glomerular filtration rate.

Stieglitz and Knight [12] and recently Stieglitz [13] have proposed the urinary excretion of sodium ferrocyanide as a test of the glomerular filtration rate. It is based on histochemical investigations by Gersh and Stieglitz,[14] who demonstrated conclusively in the rabbit that ferrocyanide is excreted entirely by glomerular action. Later, Van Slyke, Hiller and Miller,[4a] by physiologic studies, showed that the clearance of sodium ferrocyanide in the dog is equal to the glomerular filtration rate. However, there are objections to the clinical application of the ferrocyanide excretion test. 1. Clearance studies with sodium ferrocyanide on normal human subjects performed by Miller and Winkler [15] indicate that sodium ferrocyanide is reabsorbed in the human kidney. They found the ferrocyanide clearance to be about equal to the clearance of urea, which is both filtered and reabsorbed. Moreover, sodium ferrocyanide, in plasma concentrations comparable to those one can reasonably expect to be present in patients with low renal function during Stieglitz' test, caused considerable damage to the renal tubules. These observations strongly suggest that sodium ferrocyanide enters the tubules in man. 2. The ferrocyanide procedure is an excretion test, not a clearance test, and may give erroneous results because it does not take into account the concentration of the substance in the blood. Ferrocyanide is dissolved in the entire volume of extracellular fluid, of which the aqueous portion of the plasma constitutes only a small fraction. Therefore, changes in the volume of body fluid, by altering the concentration of ferrocyanide in the plasma, will affect the total urinary excretion of this compound. Because of these objections it is our opinion that ferrocyanide is unsuitable for the study of the glomerular filtration rate in man.

Of the several compounds proposed for measurement of the filtration rate in man only inulin appears to be satisfactory for clinical use. Measurements of inulin clearance until now have been restricted to research studies because of the absence of a suitable analytic technic. Previously it was usually necessary to inject large quantities of inulin

12. Stieglitz, E. J., and Knight, A. A.: Sodium Ferrocyanide as a Clinical Test of Glomerular Efficiency: Preliminary Report, J. A. M. A. **103**:1760 (Dec. 8) 1934.

13. Stieglitz, E. J.: Test of Glomerular Function with Sodium Ferrocyanide: Further Studies, Arch. Int. Med. **64**:57 (July) 1939.

14. Gersh, I., and Stieglitz, E. J.: Histochemical Studies on the Mammalian Kidney: I. The Glomerular Elimination of Ferrocyanide in the Rabbit, and Some Related Problems, Anat. Rec. **58**:349 (March) 1934.

15. Miller, B. F., and Winkler, A. W.: The Ferrocyanide Clearance in Man, J. Clin. Invstigation **15**:489 (Sept.) 1936.

to maintain the concentration at about 100 mg. per hundred cubic centimeters of plasma. Recently, a very sensitive and relatively simple colorimetric method for inulin determination was developed by Alving, Rubin and Miller.[16] By this procedure, inulin may be determined accurately at plasma concentrations as low as 5 mg. per hundred cubic centimeters. Miller, Alving and Rubin [7] showed that the inulin clearance at low plasma concentrations in normal, nephritic and hypertensive persons is an adequate measure of the glomerular filtration rate. By simplifying the procedure used by these authors we have been able to adapt the inulin clearance to practical clinical use and yet retain the accuracy that has been achieved previously in research studies. This paper presents the experimental background for the test and the technical details.

EXPERIMENTS

A study has been made of (*a*) the rate of fall in concentration of serum inulin after a single injection of 10 Gm. of inulin and (*b*) the constancy of the values for inulin clearance obtained after the injection. Experiments were performed on 2 normal subjects and on 6 persons with nephritis or some other renal disease.

Procedure.—The plan of the experiments and the technic employed were the same as have been reported in previous studies.[7]

Results.—After intravenous injection of 10 Gm. of inulin the plasma (or serum) concentration of inulin, plotted logarithmically against time, decreased at first in a curvilinear manner, later falling, however, in a linear or almost linear relation with time (charts 1 and 2). The curvilinear relation marks, presumably, the period of equilibration between the blood plasma and the extracellular fluid. The straight line relation follows because, once equilibrium has been established, the rate of fall of the level of plasma inulin is determined by the rate at which inulin is cleared from the plasma by the kidneys.

The mean concentration of plasma inulin for each period of collection of urine nearly equals the midpoint value [17] when a straight line rela-

16. (*a*) Alving, A. S.; Rubin, J., and Miller, B. F.: A Direct Colorimetric Method for the Determination of Inulin in Blood and Urine, J. Biol. Chem. **127**: 609 (March) 1939. (*b*) Alving, A. S.; Miller, B. F., and Flox, J.: Further Notes on the Colorimetric Determination of Inulin, to be published.

17. The true mean inulin plasma concentration for a given period of collection of urine is somewhat higher than the midpoint value. The mean concentration approaches the midpoint concentration as the period of urine collection is shortened. When periods of collection of urine are an hour or longer the mean concentration of inulin in the plasma may be represented by the level of inulin occurring in the

(Footnote continued on page 312)

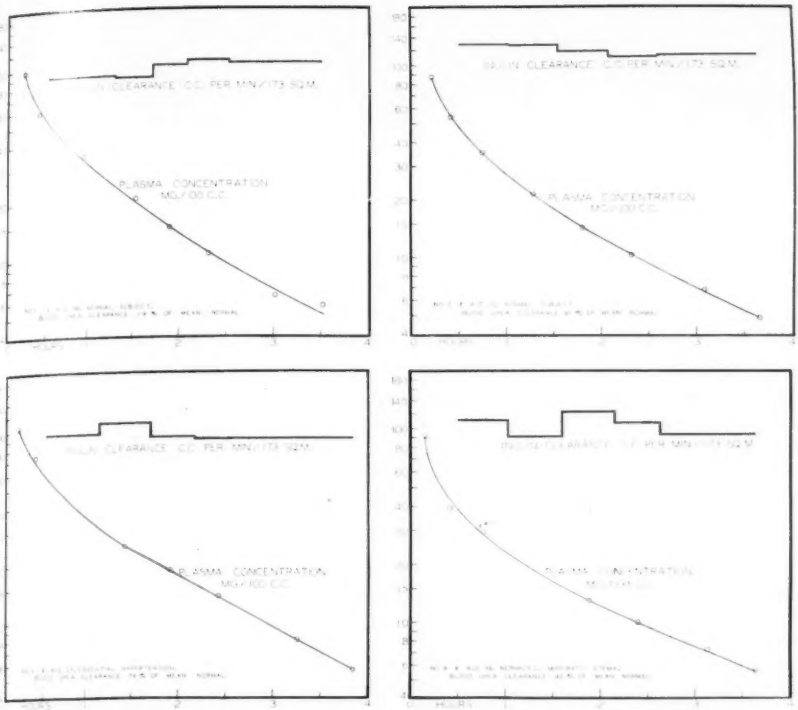

Chart 1.—Inulin clearance and blood plasma concentration after intravenous injection of 10 Gm. of inulin in persons with normal renal function.

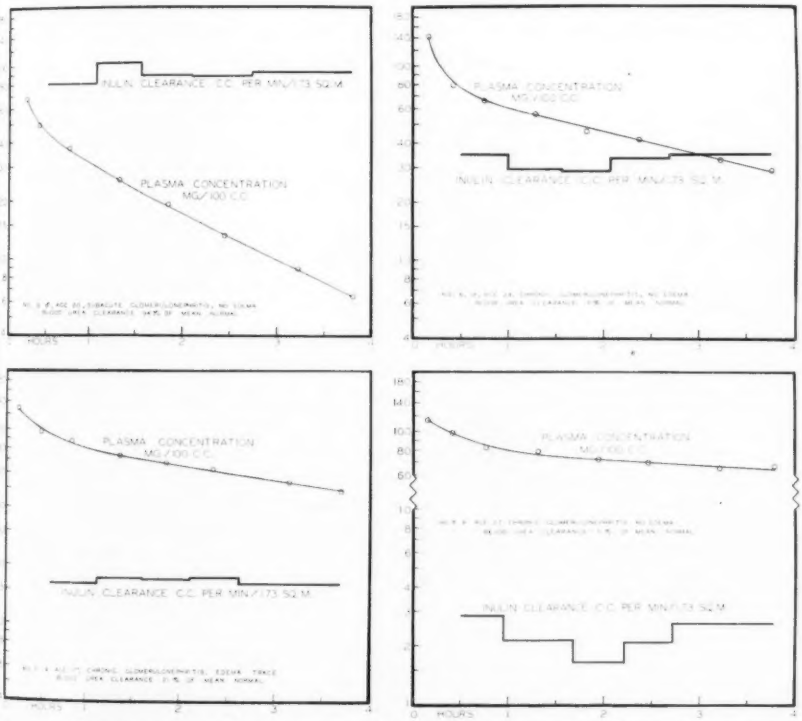

Chart 2.—Inulin clearance and blood plasma concentration after intravenous injection of 10 Gm. of inulin in patients with glomerulonephritis.

tion exists. Therefore it is apparent that determinations of inulin clearance can be performed best after the initial period of equilibration.

The period of equilibration between the plasma and the tissues varies considerably from one person to another. It is usually complete in less than one hour, but in exceptional cases, such as those in which the subjects have a massive accumulation of fluid, the period of equilibration may last for one and one-half hours after intravenous injection of inulin.

In the charts the absolute values for inulin clearances are given. It is evident that the clearance values are independent of the concentration of inulin in the plasma, even at the very low levels. (More data on this point may be found in the paper of Miller, Alving and Rubin.[7])

These results lead to the following conclusion: The clearance of plasma inulin may be measured accurately over a period of several hours after a single intravenous injection of a small quantity of inulin. In clinical tests, determination of the inulin clearance should be started one to one and one-half hours after injection of inulin. This interval gives satisfactory equilibration of inulin between the plasma and the extracellular fluid.

DESCRIPTION OF A SIMPLE CLINICAL PROCEDURE FOR MEASUREMENT OF THE GLOMERULAR FILTRATION RATE

By modification of the procedure just described, a simple test for routine clinical use has been developed. The routine test is performed best during two periods of collection of urine, one period serving as a check on the other. We perform the test as follows:

Preparation of the Subject.—The inulin clearance test may be started at any time of the day, but whenever possible it should be done in the morning. It is best to keep the subject reclining during the test. His height and weight are recorded for calculation of the surface area.

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plasma several minutes before the midpoint. For research purposes the correct mean concentration of inulin in the plasma may be determined by the following equation:

$$C_M = \frac{C_1 - C_2}{2.303 \log C_1/C_2}$$

wherein

C_M = mean inulin concentration of the plasma during any period of collection of urine.

and

C_1 and C_2 = inulin concentration of the plasma at the beginning and end, respectively, of the period of collection of urine.

It is only necessary to obtain two blood samples at different times during the straight part of the plasma inulin curve to estimate the true mean concentration. The values of C_1 and C_2 may be determined graphically in a manner similar to that described under calculation of the midpoint plasma concentration. The inulin concentration in the blood falls so slowly after equilibrium has been reached that correction for "delay time" ^{sd} is of no clinical significance except in special cases.

A light breakfast is given, usually consisting of one-half glass of milk and one slice of toast and butter (at 7:30 a. m.). Unless administration of fluid is contraindicated, it is desirable to promote a free flow of urine during the test. For this purpose the subject is given one glass of water at 6:30 a. m. and every half hour thereafter until the test is finished.

Control Samples of Blood and Urine.—A sample of blood is always obtained before inulin is injected. This sample serves to correct the subsequent analyses of blood inulin for the non-inulin chromogenic material. The control sample is analyzed in the same manner as the blood containing inulin.

A control sample of urine, on the other hand, is obtained only when it is necessary to achieve the greatest possible accuracy in testing patients with severely damaged kidneys. In cases of uremia a maximum error of 10 per cent may be introduced by ignoring the non-inulin chromogenic material in the urine. For ordinary clinical purposes the control sample of urine can be neglected even for uremic subjects. For nonuremic subjects the error is always less than 1 per cent.

Administration of Inulin.—At 8:00 a. m., 10 Gm. of inulin [18] dissolved in 100 cc. of physiologic solution of sodium chloride is injected intravenously at a rate of 10 cc. per minute. The inulin solution should be brought to body temperature before injection.[19] (Any other time convenient to the individual clinician may be chosen for the intravenous injection, provided that the schedule of fluid administration is changed correspondingly.)

Collection of Urine.—If the flow of urine is very rapid or there is good reason to believe that emptying of the bladder is complete, catheterization is unnecessary. Whenever possible, male patients should be

18. By employing the colorimetric method of Alving, Rubin and Miller [16] for analysis of inulin, the clearances may be performed in the case of the normal adult after injection of as little as 5 Gm. of inulin and in uremic patients after injection of a much smaller quantity. We have chosen to inject 10 Gm., since this is the smallest quantity which will permit accurate analyses of the blood for several hours in persons with normal renal function and anasarca. We prefer to dilute the serum filtrates rather than to change the dose of inulin for uremic patients. Should it be desirable in research studies to perform clearance tests over a longer period than three and one-half hours, a larger quantity of inulin may be administered.

19. Nontoxic sterile inulin may be obtained in ampules containing 5 Gm. of inulin in 50 cc. of physiologic solution of sodium chloride from the U. S. Standard Products Company, Woodworth, Wis. Because the inulin tends to crystallize out of solution slowly at room temperature, the ampule should be placed in boiling water until the inulin redissolves. The inulin should be shaken vigorously before heating. In the case of solutions having excessive crystallization, the time necessary for redissolving the inulin may exceed one-half hour. The solution should be perfectly clear before injection.

allowed to void their urine in the standing position. When catheterization is necessary the bladder should be washed with three 20 cc. portions of physiologic solution of sodium chloride. These washings are added to the urine and thoroughly mixed with it; this mixture is taken as the sample of urine for the period, and the inulin analyses and calculations of the urine flow are made from it. The end of the third washing of the bladder is recorded as the time of collection of urine.

The bladder is emptied one hour (or one and one-half hours in the case of a patient with massive edema) after completion of the injection of inulin, and this urine is discarded. Two consecutive hourly collections of urine are then made. The resulting samples of urine, which represent the collections for the clearance periods, are timed accurately, measured and analyzed for inulin.

It is not essential that the periods of collection of urine be exactly one hour. It is absolutely essential that the bladder be emptied completely each time and that the periods be timed accurately.

Collection of the Samples of Blood.—At the midpoint of each clearance period (one and one-half and two and one-half hours after the end of the injection of inulin in patients without anasarca) 15 cc. or more of blood is drawn by venipuncture. Every attempt should be made to collect the blood at the midpoint of each period of collection of urine, but even if the time does not correspond to the exact midpoint the proper value may be found, as will be shown later in the section on calculations.

Either blood serum or plasma (from oxalated or heparinized blood) may be employed for the analyses.

Analysis of Inulin in Blood and Urine.—It is possible by reference to charts 1 and 2 to predict the approximate concentrations of blood inulin that will be found in the "midpoint samples." This concentration will depend on (*a*) the renal function, i. e., the higher the clearance, the lower the concentration of blood inulin and (*b*) the volume of extracellular fluid in which the inulin can diffuse; thus, for patients with anasarca the value for plasma inulin will be lower than for nonedematous persons with the same level of renal function.

In order to make the proper dilution of the urine, after a protein-free filtrate has been made, one approximates the concentration of inulin in the urine as follows: A fair guess as to the percentage of renal function can usually be made from knowledge of the clinical condition of the patient or from previous tests of renal function such as the blood urea clearance, urine concentrating ability or the phenolsulfonphthalein test. This percentage times 1.25 is assumed to be the inulin clearance for the subject. The approximate concentration of inulin in the urine is found by multiplying the predicted inulin clearance by the midpoint plasma inulin concentration, obtained as has been described, and divid-

ing this product by the urine flow in cubic centimeters per minutes; thus, $C_I = \frac{U}{B} \frac{V}{}$. With these estimated urine and blood concentrations as guides, the protein-free filtrates are diluted to fall within the range of the method employed for analysis of inulin. Occasionally it may be necessary to repeat the dilutions when one has assumed a clearance which happens to lie very far above or below the patient's true functional level.

For analysis of inulin, the colorimetric method of Alving, Rubin and Miller [20] is employed. This method is simple enough to be performed with ease in any well equipped clinical laboratory. The analytic technic is the same for serum, plasma or urine. The procedure is given in brief outline here in order to give the reader some idea of the apparatus and time required for the analyses. Those who wish to employ the method should refer to the original papers, which describe the technical details.

Dextrose is removed from plasma, serum or urine by fermentation. Filtrates are prepared from the fermented samples and are diluted, if necessary, to contain between 0.002 and 0.012 mg. of inulin per cubic centimeter. Five cubic centimeters of each filtrate is placed in a special pressure-resistant glass tube and mixed with 10 cc. of freshly prepared acid-alcohol-diphenylamine reagent. The tube is heated in a vigorously boiling water bath for one hour. Up to thirty-six tubes may be carried through the analysis at one time. The tubes are cooled to room temperature by immersion in cold water. The clear blue color given by the inulin is quantitated in an Evelyn photoelectric colorimeter or a visual colorimeter. Blank analyses performed on reagents and distilled water correct for any color added by these solutions.

Calculation of the Plasma Concentration When a Sample of Blood Cannot Be Obtained at the Exact Midpoint of the Clearance Period.—If the sample of blood is not obtained at the exact midpoint, the correct value may be calculated as follows: On semilogarithm graph paper the two concentrations of blood inulin are plotted on the logarithmic coordinate against time on the linear coordinate. A straight line is drawn between the two blood concentrations. The plasma concentration corresponding to the midpoint of the clearance period is then obtained, and this value may be taken as the mean plasma concentration for the period. For ordinary clinical purposes this correction should be applied only when a sample of blood is obtained two or more minutes from the midpoint.[17]

Calculation of the Inulin Clearance (or Glomerular Filtration Rate).—The plasma (or serum) inulin clearance is calculated from the formula $C_I = U\ V/B$, in which

C_I = cc. of plasma cleared of inulin per minute per 1.73 square meters of surface area (average human subject).

U = urine inulin concentration in milligrams per hundred cubic centimeters.

20. Footnotes 7 and 16.

B = mean plasma (or serum) inulin concentration in milligrams per hundred cubic centimeters.

V = urine volume in cubic centimeters per minute.

The clearance when obtained for adults of average size by this calculation does not need further correction. However, when clearance tests are performed on children or on adults who deviate from the norm or when highest precision is desired, the urine volume should be corrected for the subject's deviation from average surface area. The proper correction factors are given by Peters and Van Slyke.[21]

The absolute inulin clearance obtained by the foregoing calculations is divided by 1.25 whenever it is desirable to express the inulin clearance (or glomerular filtration rate) in percentage of average normal.

COMMENT

The test for inulin clearance, or glomerular filtration rate, described here is a simple enough procedure to be done in almost any hospital. The test demands little from the patient and can be performed safely on very ill persons. The analytic skill required for the analyses of inulin is about the same as for any of the blood chemistry determinations in current use. Because of the simplicity of the test and the attractiveness of the idea of obtaining a well defined measurement of function of the kidney in disease there may be a tendency to exaggerate the applicability of this test. It seems to us that the inulin clearance test has an important application in clinical studies of patients in whom renal function is deranged. On the other hand, there seems little point in supplanting the entirely satisfactory urea clearance, fractional phenol-sulfonphthalein or urine concentration tests for routine diagnosis and follow-up of patients.

Estimation of the glomerular filtration rate by the inulin clearance enables one to make a number of calculations of the excretion characteristics of the kidney in disease. For example, the glomerular filtration rate minus the rate of urine flow gives the amount (in cubic centimeters) of water reabsorbed per minute by the tubules. Such a measurement has obvious applications in the study of water excretion under the influence of various diuretics or in such a disease as diabetes insipidus.

Furthermore, whenever another substance is as freely filtrable from the plasma as inulin [22] its clearance value in relation to the inulin clearance permits important deductions. If the clearance of a compound is

21. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 568.

22. The "filtrability" of a substance is usually determined by measuring its diffusibility through membranes of known pore size by means of an ultrafiltration apparatus such as has been described by P. H. Lavietes (Anaerobic Ultrafiltration, J. Biol. Chem. **120**:267 [Aug.] 1937).

lower than that of inulin, the compound has been reabsorbed in the tubules. The extent of reabsorption is calculated very simply as: (inulin clearance—clearance of "X")/inulin clearance. For example, with an adequate urine flow, the mean plasma urea clearance for a normal man of average size is 70 cc. per minute.[5a] It is known that urea is filtered from the plasma as readily as inulin. Therefore, the reabsorption of urea is calculated as $\frac{125-70}{125} \times 100$, which equals 44 per cent. Now consider an example which illustrates the striking changes that may be observed in disease when simultaneous urea and inulin clearances are performed. McCance and Widdowson[23] made such a comparison in cases of diabetic acidosis and observed a complete derangement of this normal relation. Calculation of the tubular reabsorption of urea from the data on one of these subjects follows: In this patient the inulin clearance was 31.8 cc. per minute and the urea clearance 3.6 cc. per minute. Therefore the per cent reabsorption was $100 \times \frac{31.8-3.6}{31.8}$, or 89 per cent of the filtered urea. This striking derangement of the normal activity of the tubular system with respect to urea could have been demonstrated convincingly only by comparing the urea clearance with the filtration rate. McCance and Widdowson further demonstrated that the tubules in a patient with diabetic acidosis may be abnormal with respect to the excretion of exogenous creatinine and the reabsorption of sodium, chloride and dextrose.

Important calculations may be made on the excretion characteristics of dextrose. Normally the clearance of dextrose is zero, indicating complete tubular reabsorption of this compound. In diabetes, the clearance becomes positive as glycosuria develops. The actual quantity of dextrose reabsorbed per minute may be calculated as follows: (the inulin clearance minus the dextrose clearance) multiplied by the concentration of dextrose in the blood plasma is equal to the amount of sugar reabsorbed. As was shown by Shannon and Fisher,[5b,e] this value for the normal kidney approaches a well defined limit which equals the maximal reabsorptive capacity of the tubular system with respect to dextrose. A maximal reabsorptive capacity has been demonstrated also for ascorbic acid.[24]

Recently, Coombs and Talbott,[25] by comparing the clearance of uric acid with the inulin clearance, studied the ability of gouty patients to excrete uric acid.

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23. McCance, R. A., and Widdowson, E. M.: Functional Disorganization of the Kidney in Disease, J. Physiol. **95**:36 (Jan.) 1939.

24. Ralli, E. P.; Friedman, G. J., and Rubin, S. H.: The Mechanism of the Excretion of Vitamin C by the Human Kidney, J. Clin. Investigation **17**:765 (Nov.) 1938.

25. Coombs, F. S., and Talbott, J. H.: The Mechanism of Uric Acid Elimination by the Kidney, J. Clin. Investigation **18**:490 (July) 1939.

When a substance has a clearance higher than that of inulin, it is excreted presumably partly or completely by the renal tubules. Exogenous creatinine is such a substance, and comparison of its clearance with that of inulin [6c] demonstrated its true mode of excretion by the human kidney and proved the error involved in Rehberg's assumption that the clearance of exogenous creatinine may be employed for clinical study of the filtration rate. When the excretion of endogenous creatinine was studied in man [9] it appeared that this compound was excreted in part by the tubules in cases of advanced renal damage, whereas in the normal kidney such tubular secretion was not constantly present. Phenolsulfonphthalein, diodrast and hippuran are other substances which are excreted largely by the tubules, as is shown by comparison of their clearances with the inulin clearance.[5d]

It is hoped that application of the inulin clearance measurement in various clinical conditions will give a better understanding of the deranged renal function associated with them. For example, the reason for the elevated level of blood urea associated with Addison's disease has not been elucidated completely. Also, the role of the kidney in the so-called extrarenal azotemias has not been studied extensively by modern technics. Many of these interesting derangements of the renal excretory mechanism occur in diseases which lie outside the province of investigators of "renal disease." It is possible with the method outlined in this paper to obtain precise information of certain excretion characteristics of the kidney in all diseases in which derangement of renal function is suspected. By doing so, it should be possible in the future to give precise estimates of the changes which have occurred in specific functions and anatomic sections of the nephron and thereby avoid descriptions of the pathologic physiology of the kidney in such vague terms as "impairment of kidney function."

950 East Fifty-Ninth Street.

PURPURA HAEMORRHAGICA DUE TO THE ARSPHENAMINES

SENSITIVITY IN PATIENTS AS INFLUENCED BY VITAMIN C THERAPY

ERNEST H. FALCONER, M.D.

NORMAN N. EPSTEIN, M.D.
AND
EDITH S. MILLS, M.A.
SAN FRANCISCO

Since 1933 we have had an opportunity to study 7 patients showing reactions accompanied by thrombopenic purpura following arsphenamine therapy. These patients have submitted to further injections of arsphenamine preparations; thereby we have been allowed to reproduce experimentally their attacks of purpura. An opportunity has thus been afforded for study of the effects of oral and parenteral administration of vitamin C on this type of sensitivity.

Our interest in the effect of vitamin C on purpura due to administration of neoarsphenamine was stimulated by reports in the literature that tended to show a relationship between vitamin C deficiency and arsphenamine sensitivity and also by reports of the clinical use of vitamin C as an agent to ameliorate the toxic effects of the arsphenamines. We have been interested also in several reports concerning the therapeutic value of ascorbic acid in the treatment of patients having idiopathic thrombopenic purpura.

In 1935 Sulzberger and Oser [1] published results, obtained from experiments on guinea pigs, which tended to show that animals on a diet deficient in vitamin C were more easily sensitized to neoarsphenamine by intracutaneous injection of the drug than were animals on a diet to which a daily dose of 2 mg. of vitamin C had been added. Streitmann and Wiedmann [2] reported similar experiments in which

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From the Department of Medicine and the Department of Dermatology of the University of California Medical School.

1. Sulzberger, M. B., and Oser, B. L.: Influence of Ascorbic Acid of Diet on Sensitization of Guinea Pigs to Neoarsphenamine, Proc. Soc. Exper. Biol. & Med. **32**:716, 1935.

2. Streitmann, B., and Wiedmann, A.: Biologische Pruefungen von Arsenobenzolderivaten: II. Vergleichende Untersuchungen ueber die Sensibilisierungsfaehigkeit einzelner Arsenobenzolderivate, Arch. f. Dermat. u. Syph. **175**:696, 1937.

guinea pigs receiving winter diets (dry fodder) plus vitamin C were less easily sensitized to neoarsphenamine than were those on the winter diets alone. Cormia [3] reported experiments indicating that guinea pigs on diets low in vitamin C exhibited reactions to intracutaneous injections of neoarsphenamine of longer duration and of greater severity than the reactions of those on an adequate diet. In animals on a diet containing 50 Gm. of ascorbic acid daily, he found that sensitization to arsphenamine was difficult to induce. Cormia [4] reported 6 cases in which the onset of dermatitis followed the administration of arsphenamine and in which improvement of the eruption occurred after the administration of large doses of vitamin C. In 2 or 3 cases of dermatitis, the arsphenamine preparation that had previously caused reactions was tolerated without untoward results after large preliminary doses of vitamin C had been given intravenously.

Experimentation on animals with results exactly opposite to those already described were reported by Chapman and Morrell,[5] who found that guinea pigs on a diet low in vitamin C became sensitive to arsphenamine less readily than the animals on a normal diet.

Recent carefully controlled studies by Cohen [6] showed no difference in sensitivity to neoarsphenamine between guinea pigs on a diet low in vitamin C and those on what he termed "a tooth-protective ration." Cohen employed the microscopic appearance of developing teeth in the guinea pig as the criterion for insufficient vitamin C in the ration. He has stated that this is the most sensitive and reliable test for vitamin C deficiency in the guinea pig.

In connection with the results of investigators using vitamin C clinically to diminish the toxic reaction of the arsphenamines, the report of Friend and Marquis [7] is of interest. These authors determined the vitamin C content of the blood of patients who had exhibited signs of sensitiveness to the form of arsphenamine they were receiving. The average reading for untreated patients was 0.64 mg. per hundred cubic centimeters of blood. The average reading for patients receiving treat-

3. Cormia, F. E.: Experimental Arsphenamine Dermatitis: The Influence of Vitamin C in the Production of Arsphenamine Sensitiveness, Canad. M. A. J. **36**:392, 1937.

4. Cormia, F. E.: Experimental Arsphenamine Sensitization: Further Observations on the Reactions to Arsphenamine in Guinea Pigs Given Staphylococcus Toxin, and in Guinea Pigs with Induced Streptococcal Infection, J. Invest. Dermat. **1**:199, 1938.

5. Chapman, C. W., and Morrell, C. A.: Influence of Vitamin C on Development of Skin Sensitivity to Neoarsphenamine in the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **32**:813, 1935.

6. Cohen, M. B.: Vitamin C Deficiency: Sensitivity to Neoarsphenamine and Anaphylactic Shock, J. Allergy **10**:15, 1938.

7. Friend, D. G., and Marquis, H. H.: Arsphenamine Sensitivity and Vitamin C, Am. J. Syph., Gonor. & Ven. Dis. **22**:239, 1938.

ment with the arsphenamines was 0.63 mg. per hundred cubic centimeters. The readings for 5 patients with arsphenamine reactions varied from 0.13 to 0.35 mg., with an average for the group of 0.25 mg. per hundred cubic centimeters of blood. Their conclusion was that a low vitamin C content in the plasma was the result of the toxic reaction to the arsphenamines rather than a predisposing factor to such reactions.

Dainow [8] stated that vitamin C increased a patient's tolerance to the arsphenamines; he stated further that his patients with low contents of vitamin C in their diet showed lack of tolerance to the arsphenamines. He concluded that vitamin C prevents the oxidation of arsphenamine in the tissues and thereby decreases its toxic action in the body.

Reports concerning the influence of vitamin C in controlling the hemorrhages in cases of idiopathic thrombopenic purpura indicate conflicting opinions as to its therapeutic effect. Böger and Schröder [9] described a patient of their series, an elderly man with thrombopenic purpura who after four daily injections of 150 mg. of ascorbic acid given intravenously ceased bleeding. After one month of further daily injections of 100 mg. of ascorbic acid, the platelet count rose to 304,000 per cubic millimeter. Winckelmann [10] treated 1 patient with idiopathic thrombopenic purpura by administering large doses of ascorbic acid, with apparently satisfactory results. This author attributed the reported failures as due to the use of too small doses of vitamin C. He advocated using a dose sufficient to saturate the tissues and the urine. He mentioned the use of doses as high as 1,000 to 1,500 mg. of ascorbic acid daily.

Vogt [11] reported 2 cases of thrombopenic purpura, the diagnosis in 1 case being doubtful, in which daily treatment was given, with 2 to 6 cc. of a solution of ascorbic acid (100 to 300 mg. of ascorbic acid crystals), with good results. He believed that vitamin C strengthened the capillaries and prevented capillary leakage of blood. Miller and Rhoads [12] treated 4 patients with idiopathic thrombopenic purpura by administration of vitamin C. For 2 of the 4 patients the excretion of ascorbic acid was measured quantitatively to test the relative degree of saturation with vitamin C. In both patients clinical improvement

8. Dainow, I.: Intolérance aux arsénobènzenes et vitamin C, Presse méd. **45**: 1670, 1937.

9. Böger, A., and Schröder, H.: Ueber die Stillung schwerster Blutungen bei allen Foramen der hämorrhogischen Diathese und der Hemophilie durch parenterale Zufuhr von C-vitamin (Cebion Merck), München. med. Wchnschr. **81**: 1335, 1934.

10. Winckelmann, H.: Zur Vitamin C Behandlung von hämorrhagischen Diathesen, Med. Klin. **34**:906, 1938.

11. Vogt, E.: Ueber die Behandlung gynäkologischer Blutungen mit Vitamin C, München. med. Wchnschr. **82**:263, 1935.

12. Miller, D. K., and Rhoads, C. P.: Ascorbic Acid in the Treatment of Thrombocytopenic Purpura, J. Clin. Investigation **15**:462, 1938.

and an increase in thrombocytes were associated with an increased urinary output of ascorbic acid. Böger and Morton [13] reported that the administration of 200 mg. daily of ascorbic acid to patients with thrombopenic purpura produced a marked rise in the number of platelets, with a decrease in bleeding.

Walther [14] mentioned 3 patients with thrombopenic purpura who received from 100 to 500 mg. of ascorbic acid daily, with no improvement that he could attribute directly to vitamin C.

Janet Vaughan [15] reported a case of idiopathic thrombopenic purpura in which the patient was treated for five days with daily intravenous injections of 80 mg. of ascorbic acid, with no improvement. Then from September 29 to November 2 the patient received 80 mg. orally, which was increased to 160 mg. daily from November 2 to December 13, with no improvement. Davidson [16] treated 3 patients with thrombopenic purpura by intravenous injections of vitamin C, without improvement. Wright and Lilienfeld [17] made a thorough study of the therapeutic possibilities of vitamin C (ascorbic acid). Their series included 3 patients with thrombopenic purpura. One of these patients, a woman aged 45, with a history of bleeding from the gums and nasal mucosa, was under observation for forty-five days. For seven days before admission to the hospital she received orally 90 mg. of ascorbic acid daily. During the next thirty-eight days she received 100 mg. daily, intravenously, except for two days when none was given and one day when 200 mg. was administered. The patient appeared to be improving up to the thirtieth day, at which time she had a relapse while she was receiving a daily intravenous dose of 100 mg. of ascorbic acid. The other 2 patients were children who received a daily intravenous injection of 100 mg. of ascorbic acid, 1 for three weeks and the other for fourteen days. No definite improvement was evident in either patient.

METHOD

Six patients known to be sensitive to neoarsphenamine and 1 patient sensitive only to bismarsen were selected for this experimental study. These patients having been tested previously with varying doses of the arsphenamines, we had definite data concerning their sensitivity, and we believed the degree of sensitivity could be roughly estimated in each case. The previous reactions exhibited by these

13. Böger, A., and Morton, W.: Vitamin C und Blut, München. med. Wchnschr. **82**:899, 1935.

14. Walther, G.: Misserfolge bei Vitamin C Therapie, Med. Klin. **34**:260, 1938.

15. Vaughan, J. M.: Treatment of Thrombocytopenic Purpura, Brit. M. J. **2**: 842, 1937.

16. Davidson, L. S. P.; Davenport, C., and Rabagliati, D. S.: Discussion on Purpuric Conditions in Man and Animals, Proc. Roy. Soc. Med. **30**:715, 1937.

17. Wright, I. S., and Lilienfeld, A.: Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid) with Especial Reference to Its Effect on Capillary Fragility, Arch. Int. Med. **57**:241 (Feb.) 1936.

patients following the administration of neoarsphenamine or bismarsen consisted of toxic reactions varying from almost no symptoms in 1 case to marked prostration, nausea, vomiting, rapid pulse, chills and malaise and was followed in each instance by thrombopenic purpura. Up to this time no vitamin C had been administered to any of these patients before their reactions. In 1 case, following purpura and other hemorrhagic phenomena, vitamin C was administered. The diet of each patient was inquired into carefully, and for only 1 patient was the intake of vitamin C deemed inadequate.

The blood counts were done with pipets standardized by the United States Bureau of Standards. Hemoglobin estimations were made with the Sahli instrument, as modified by Osgood and Haskins.[18] With this instrument 13.8 Gm. per hundred cubic centimeters of blood is considered normal. Platelet counts were made by the method of Rees and Ecker.[19] The capillary fragility tests were made with the Dalldorf [20] instrument. In each instance the reading was made after one minute of negative pressure. The amounts taken and the intervals during which these patients took vitamin C orally and intravenously varied considerably, but these amounts and the time intervals are recorded in the case reports which follow.

REPORT OF CASES

CASE 1.—G. S., a woman aged 52, was being treated in the syphilitic clinic in 1933 and 1934, at which time she showed an initial sensitivity to neoarsphenamine after her first intravenous injection of 0.3 Gm. After the second injection of 0.15 Gm. of the drug one week later, she had a toxic reaction followed by purpura haemorrhagica. Her case was reported in 1936 [21] as G. N., case 2.

On May 29, 1934, through an oversight on the part of the physician in charge of her treatment, she was given an intravenous injection of 0.3 Gm. of neoarsphenamine. An immediate toxic reaction followed, with nausea, vomiting, chills and general malaise, and within twenty-four hours purpuric areas appeared in the buccal mucous membranes. On June 4, one week later, she received another injection of neoarsphenamine (0.3 Gm.), which was followed immediately by a toxic reaction and after twenty-four hours by a generalized purpuric eruption. We have no record of her platelet count before these two intravenous injections of neoarsphenamine; but when she reported to the hematologic clinic on June 6, the platelet count was 10,000 per cubic millimeter, and the bleeding time (Duke) was sixteen minutes.

On Feb. 8, 1935, approximately nine months later, an intravenous injection of 0.1 Gm. of neoarsphenamine was administered in order to ascertain the state of the patient's sensitivity. Immediatelly after the injection her face became flushed, and she had nausea, vomiting and severe pains in the lumbar region. About thirty minutes after the injection a chill supervened, and at the one hour period

18. Osgood, E. E., and Haskins, H. D.: A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, J. Biol. Chem. **57**:107, 1923.

19. Rees, H. M., and Ecker, E. E.: An Improved Method for Counting Blood Platelets, J. A. M. A. **80**:621 (March 3) 1923.

20. Dalldorf, G.: A Sensitive Test for Subclinical Scurvy in Man, Am. J. Dis. Child. **46**:794 (Oct.) 1933.

21. Falconer, E. H.; Epstein, N. N., and Wever, G. K.: Purpura Haemorrhagica Following the Administration of Neoarsphenamine: Reaction to Neoarsphenamine Compared with Reaction to Mapharsen, Arch. Int. Med. **58**:495 (Sept.) 1936.

the platelet count had fallen from 300,000 before the injection to 20,000. At this time there was bleeding from the nasal mucosa, and purpuric lesions were appearing over the lower extremities with a few hemorrhagic blebs in the buccal mucous membranes. On March 8, about nine days after the injection, the platelet count had increased to 230,000 and the purpuric lesions had nearly disappeared.

After three years, during which time the patient had been free of symptoms and had received no treatment with arsenicals, she returned on March 12, 1938, for further tests to determine the status of her sensitivity to neoarsphenamine. We planned to study the effects of vitamin C therapy on this sensitivity, par-

TABLE 1.—*Data in Case 1*

Date	Time	Platelet Count*	White Cell Count
3/12/38	Before administration of neoarsphenamine	250,000	8,200
	15 minutes after	110,000	6,300
	30 minutes after	120,000	7,100
	60 minutes after	120,000	8,400
	2 hours after	80,000	9,300
3/14/38	2 days after	180,000	8,350
3/16/38	4 days after	210,000	6,750
3/21/38	Before administration of neoarsphenamine	260,000	7,950
	15 minutes after	150,000	4,900
	30 minutes after	110,000	5,100
	60 minutes after	150,000	5,900
	2 hours after	160,000	6,100
	2½ hours after	30,000	6,050
3/22/38	24 hours after	110,000	8,500
3/25/38	4 days after	270,000	8,400
5/24/38	Before administration of neoarsphenamine	390,000	5,800
5/31/38	Before administration of neoarsphenamine	290,000	6,500
	15 minutes after	100,000	1,900
	30 minutes after	95,000	7,700
	60 minutes after	60,000	4,800
	2 hours after	90,000	3,900
	5 hours after	110,000	6,000
	7 hours after	120,000	6,250
6/ 1/38	26 hours after	20,000	7,800
6/ 2/38	2 days after	110,000	5,400
6/ 3/38	3 days after	150,000	8,200
6/ 4/38	4 days after	220,000	6,300
6/ 7/38	7 days after	360,000	8,900

* The platelet counts from March 12 to 16 inclusive were made after the administration of 0.01 Gm. of neoarsphenamine, before therapy with ascorbic acid; the counts from March 21 to 25 inclusive were made after the administration of 0.015 Gm. of neoarsphenamine, before therapy with ascorbic acid; the counts from May 31 to June 7 inclusive were made after the administration of 0.0075 Gm. of neoarsphenamine, after nine weeks' therapy with ascorbic acid.

ticularly with respect to its influence on the toxic reaction and purpuric phenomena which invariably followed the administration of neoarsphenamine. On the day of her return the patient was given an intravenous injection of 0.01 Gm. of neoarsphenamine, an amount one-tenth the size of the dose that had caused a sharp reaction three years before. Immediately after this injection she had a constitutional reaction and purpuric phenomena of the same type as those already described as following the administration of 0.1 Gm. of neoarsphenamine on Feb. 8, 1935, with the exception that the symptoms were milder, the purpuric eruption being confined to the lower extremities and the lesions consisting of fine, scattered petechiae, which could be well made out with the aid of a hand lens. The effect on the platelet level is shown in table 1.

Nine days later, on March 21, we administered a second injection of neoarsphenamine, increasing the dose slightly to 0.015 Gm. An immediate toxic reaction occurred, followed by the appearance of purpuric lesions over the upper and lower extremities two and one-half hours after the injection. At that time the

platelet count showed a drop from 260,000 before the injection to 30,000. All the sensitivity phenomena were intensified with this slightly larger dose of neoarsphenamine. We felt that if we now gave the patient sufficient vitamin C therapy to saturate the tissues, and if we repeated the dose of 0.01 Gm. of neoarsphenamine, which had produced a mild reaction, we could readily assess the value of vitamin C as a protective agent capable of diminishing the toxic symptoms of neoarsphenamine and of preventing the development of purpura through inhibiting capillary fragility. At this time, as the next step in the experiment, the patient was given a list of the natural sources of vitamin C and was instructed concerning a diet with an abundance of this vitamin, from two to three glasses of orange juice daily being included. After one month of this regimen, 1 tablet of ascorbic acid, containing 0.25 mg., three times per day was added, to be taken by mouth along with the diet. After three weeks of this diet, plus 75 mg. of ascorbic acid taken orally each day, additional vitamin C in the form of 100 mg. of ascorbic acid was injected intravenously every third day for fifteen days. At the end of nine weeks of increasing the vitamin C intake, we felt that the tissues were well saturated with vitamin C, a condition which, should it prove efficient in diminishing sensitivity to neoarsphenamine, would allow the patient to receive a dose of 0.01 Gm. of the drug with a minimum of reaction and slight, if any, purpuric or hemorrhagic phenomena. It will be recalled that on March 12, after the administration of 0.01 Gm. of neoarsphenamine, the patient had a relatively mild toxic reaction, with scattered, fine petechiae over the lower extremities. We were entirely unprepared for the startling reaction that followed our attempt to give 0.01 Gm. of neoarsphenamine on May 31. At 8 a. m. the platelet count was 290,000. At this time 100 mg. of ascorbic acid was administered intravenously. One hour later 100 mg. was given subcutaneously and was followed by the intravenous injection of neoarsphenamine. As soon as the solution began to flow into the vein, the patient became flushed over the face and neck. She complained of a smothering sensation; the pulse became rapid and feeble; as collapse was imminent, the needle was withdrawn after 0.0075 Gm. of the drug had been administered. The blood pressure, which had been 130 systolic and 80 diastolic before the injection, fell rapidly to 80 systolic and 60 diastolic; and as the needle was withdrawn the patient passed quickly into a state of profound shock. The radial pulse could not be felt, and the extremities were cold and cyanotic. Restorative measures were administered in succession, beginning with application of heat to the body and followed by two subcutaneous injections of 1 cc. each of epinephrine (1:1,000) and intramuscular injection of 0.5 cc. of caffeine with sodium benzoate. After one hour, 1 liter of 5 per cent dextrose solution, to which was added 1 cc. of epinephrine (1:1,000), was administered intravenously. The platelet count dropped to 100,000 fifteen minutes after the drug had been administered; at one hour the count was 60,000, and purpuric lesions were appearing over the neck, the upper part of the chest, the arms and the lower extremities (table 1; fig. 1). After eight hours the patient felt recovered from shock and insisted on being taken home. On the following morning we called at her home, feeling much concerned about her condition. As we entered her room, the sight presented was astonishing. On the floor were several heaps of towels and cloths soaked with blood. The bed sheets and pillow covers were saturated with large blood stains. Wrapped about the patient's head was a large bath towel saturated with blood. All this bleeding came from the tiny needle punctures in the lobe of the ear, the punctures having been made the previous day at the laboratory. As these punctures were still oozing, the patient was sent by ambulance to the hospital where pressure and thromboplastin applied locally

checked the bleeding. She recovered rapidly in three days without any special treatment and was discharged from the hospital. The platelet count at entry was 20,000; at discharge, 150,000, and at the end of one week after administration of the drug, 360,000 (table 1). The red cell count dropped in four days after injection from 5,300,000 to 3,710,000. The hemoglobin value dropped from 12.88 Gm. (94 per cent) to 10.49 Gm. (78 per cent).

Comment.—The results of the experiment on this patient were so striking and dramatic that comment seems scarcely necessary. However, some features deserve brief mention, particularly her sensitivity to neoarsphenamine. This sensitivity appeared to be little changed in the three year period since Feb. 18, 1935, when she was given 0.1 Gm. of neoarsphenamine, the administration of which was followed by a

Fig. 1 (case 1).—Photograph showing ecchymoses following administration of 0.0075 Gm. of neoarsphenamine, after nine weeks of preliminary therapy with vitamin C.

toxic reaction and a purpuric eruption. The injections of neoarsphenamine on March 12 and 21, 1938 appeared to increase her sensitivity markedly; and the subsequent nine weeks of abundant intake of vitamin C, in both the natural and the crystalline forms, did not reduce this sensitivity, compared with her previous reactions. In fact, it would appear as if the vitamin C intake actually enhanced her sensitivity to neoarsphenamine. This conclusion, however, is not warranted without an adequate control experiment, which was obviously not possible in this type of experiment.

The pronounced hemorrhagic features of her last reaction, May 24, 1938, as evidenced by the drop in the hemoglobin value and the red cell count over a period of four days, were far in excess of those observed at the six previous reactions studied by us, although with two of these

reactions the platelet count fell to lower levels than on May 24. On June 4, 1934, after the administration of 0.3 Gm. of neoarsphenamine, the platelet count dropped at the end of the second day to 10,000; on Feb. 28, 1935, one hour after the administration of 0.1 Gm. of neoarsphenamine, the platelet count dropped to 20,000, and two days later it dropped to 10,000.

To one interested in the study of purpura haemorrhagica, this is an important observation, suggesting as it does that the platelet level in itself is not the determining factor causing hemorrhage, but that rather loss of tone in the capillary bed is the direct factor influencing the degree of bleeding that takes place from the capillaries.

TABLE 2.—*Data in Case 2*

Date	Time	Platelet Count*	White Cell Count
1/21/37	Before administration of neoarsphenamine	290,000	6,200
	15 minutes after	50,000	.....
	30 minutes after	30,000	.....
	45 minutes after	30,000	.....
	60 minutes after	20,000	.....
	5 hours after	20,000	7,100
1/22/37	30 hours after	30,000	7,450
1/26/37	5 days after	50,000	7,300
1/28/37	7 days after	150,000	7,500
2/ 3/37	13 days after	450,000	9,450
1/12/38	Before administration of neoarsphenamine	310,000	8,000
	15 minutes after	90,000	8,400
	30 minutes after	70,000	8,500
	45 minutes after	90,000	9,800
	60 minutes after	90,000	9,700
	8 hours after	120,000	11,500
1/13/38	24 hours after	25,000	5,400
	30 hours after	60,000	5,500
1/14/38	2 days after	80,000	7,300
1/20/38	8 days after	310,000	7,400
1/22/38	10 days after	390,000	7,900

* The platelet counts from Jan. 21 to Feb. 3, 1937 inclusive were made after the administration of 0.0075 Gm. of neoarsphenamine, before therapy with ascorbic acid; the counts from Jan. 12 to 22, 1938 inclusive were made after the administration of 0.0001 Gm. of neoarsphenamine, after eight weeks' therapy with ascorbic acid.

CASE 2.—E. G., a woman aged 44, had previous reactions which had shown her to be very sensitive to neoarsphenamine. On Jan. 21, 1937 we gave her an intravenous injection of 0.0075 Gm. of neoarsphenamine to determine the degree and intensity of her reaction to this small amount of the drug. While she was receiving the injection her face and neck became flushed, then cyanotic. She felt a sense of suffocation. After the needle was withdrawn, nausea and vomiting occurred; the hands and feet became cold and the pulse rapid. Fifteen minutes after the injection the platelet count had dropped from 290,000 before injection to 50,000 (table 2), and at the end of thirty minutes the number of platelets had fallen to 30,000 per cubic millimeter. The reaction was marked, but the acute symptoms subsided in about two hours. On the following day the neck, the shoulders, the anterior portion of the chest and the extremities were covered with a petechial eruption. The oral mucous membranes showed a few hemorrhagic blebs; there was a small amount of uterine bleeding, and the urine showed many red blood cells.

Five days after this injection of neoarsphenamine the platelet count was 50,000; on the thirteenth day it was 450,000 (table 2).

On November 15 the patient was placed on a diet containing an abundance of fresh vegetables and, in addition, two glasses of orange juice daily. After twenty-five days 4 tablets daily by mouth were added to the diet, each tablet containing 25 mg. of ascorbic acid (500 international units). On Jan. 3, 1938, twenty-one days after administration of the tablets was begun, intravenous injection of an additional 100 mg. of ascorbic acid was instituted. She received five such doses at two day intervals.

With this preparation of approximately eight weeks of vitamin C therapy, the patient received on January 17 an intravenous dose of 0.0001 Gm. of neoarsphenamine. This amount was dissolved in 10 cc. of distilled water and injected slowly. Before she had received half the dose, her face and neck became flushed; she felt "as if she were choking," and the pulse became extremely rapid. At the

Fig. 2 (case 2).—Photograph showing large ecchymotic areas the development of which followed administration of 0.0001 Gm. of neoarsphenamine, after preliminary therapy with vitamin C.

end of the injection, prostration was marked; she had a severe headache and vomited. Fifteen minutes after the injection the platelet count had fallen from 310,000 before injection to 90,000; at the end of thirty minutes the count was 70,000. Eight hours after the injection of neoarsphenamine the patient was sufficiently recovered to eat a light repast with a cup of coffee, after which the platelet count rose slightly (table 2). On the following day the platelet count was 25,000. A fine petechial eruption covered the upper part of the chest, the shoulders and the upper and lower extremities. Over both calf regions were ecchymotic areas about 3 by 4 cm. Forty-eight hours after the injection the patelet count was 80,000; the patient complained of feeling very weak, with generalized pain over the body. Eight days after the injection there were large ecchymotic areas over the calf muscles of both legs (fig. 2).

Comment.—This patient was known to be very sensitive to neoarsphenamine, but we believed the dose administered after preliminary vitamin therapy was so small as to preclude anything but a mild reaction. We felt that the preliminary vitamin C therapy might eliminate the toxic reaction and purpuric manifestations entirely. The rapid and severe reaction that followed this small dose of neoarsphenamine surprised us greatly and left us with the definite impression that vitamin C therapy had no effect in diminishing sensitivity to neoarsphenamine in this patient nor in ameliorating the toxic effects of the drug.

It should be noted that the time interval between the two doses of neoarsphenamine described in this experiment was approximately one year and that no neoarsphenamine had been administered between the doses mentioned; there was no chance for sensitization to become enhanced during the interval by reason of administration of any of the arsenicals, with the exception of mapharsen, to which the patient never showed evidences of sensitization.

Case 3.—A. LaG., an obese woman aged 48, showed a marked reaction to bismarsen accompanied by thrombopenia and purpura, but she showed no reaction and no purpuric manifestations after administration of neoarsphenamine. When 0.1 Gm. of sulfarsphenamine was given intravenously, this patient went into a state of profound shock, pulmonary edema rapidly supervened, and after twenty-four hours mild bronchopneumonia occurred, from which she made a satisfactory recovery after eleven days in the hospital.

On Dec. 30, 1938 she was given a dose of 0.1 Gm. of bismarsen intramuscularly. This occurred before she had received 0.1 Gm. of sulfarsphenamine intravenously, and is recounted here to indicate her reaction to birmarsen for later comparison. The platelet count before this injection was 570,000 at one and one-half hours; after the injection it was 210,000. Immediately after receiving the drug she became pale and nauseated; the pulse was rapid and feeble, and the extremities were cold. At one and one-half hours, a chill occurred which necessitated a subcutaneous injection of 1 cc. of epinephrine (1:1,000). The platelet count rose after the injection of epinephrine, and in one-half hour the count was 320,000 per cubic millimeter. On the following day the platelet count was 60,000, and there was a marked purpuric eruption over the shoulders, the anterior part of the chest, the abdomen and the upper and lower extremities. On the sixth day after the injection the platelet count was 320,000, and the patient had recovered from her toxic reaction. About six months after the reaction just described (June 22, 1939), the patient reported for further studies of the effect of vitamin C therapy on sensitivity. Before therapy was started, she had a vitamin C level in the plasma of 0.63 mg. per hundred cubic centimeters of blood. She received 100 mg. of ascoribc acid intravenously, and on the following day she began to take 4 tablets daily of ascorbic acid by mouth, each tablet containing 25 mg. The tablets were given daily from June 22 to July 12; the intravenous injection of vitamin C, the administration of 100 mg. of ascorbic acid, was performed every second day during this period, in addition to including in her diet two oranges daily. The level of vitamin C in her blood plasma during this period is recorded in table 3. On July 10 the vitamin C in the plasma was 1.20 mg. per hundred cubic centimeter of blood. On July 12 it was 1.01 mg. On this date she received 100 mg. of ascorbic acid intravenously at 9 a. m.; at 9:30 a. m., 0.075 Gm. of

bismarsen was injected in the left buttock. At 9:45 the face was flushed, and the "gums throbbed." A slight suffocating sensation was felt at 10 a. m. Thirty minutes after the injection there was severe "backache," and at 10:15 a. m. vomiting and marked prostration. At 10:50 a. m. a chill came on, and the vomiting continued for five hours after the injection of bismarsen. Six hours after the injection, epistaxis appeared and also slight uterine bleeding, although her menstrual flow had ceased on June 26. About ten hours after the injection of bismarsen bleeding occurred from the needle puncture in the lobe of the left ear. On the following day, July 13, a purpuric eruption was present over the neck, the shoulders, the anterior

TABLE 3.—*Data in Case 3*

Date	Time	Platelet Count*	White Cell Count	Plasma Vitamin C Content, Mg. per 100 Cc. of Blood
12/30/38	Before administration of bismarsen..	570,000	9,200	....
	15 minutes after.....	510,000	7,800	....
	30 minutes after.....	460,000	16,000	....
	60 minutes after.....	300,000	12,100	....
	1½ hours after.....	210,000	9,300	....
	2 hours after.....	320,000	9,100	....
	3 hours after.....	170,000	8,400	....
12/31/38	24 hours after.....	60,000	11,500	....
	34 hours after.....	80,000	12,100	....
1/ 3/39	4 days after.....	110,000	15,750	....
1/ 4/39	5 days after.....	160,000	19,100	....
1/ 5/39	6 days after.....	320,000	17,300	....
6/22/39	Before administration of bismarsen..	360,000	11,300	0.63
6/24/39	Before administration of bismarsen..	310,000	16,100	....
6/26/39	Before administration of bismarsen..	400,000	12,600	0.75
6/28/39	Before administration of bismarsen..	360,000	11,900	0.87
6/30/39	Before administration of bismarsen..	370,000	10,700	0.93
7/ 5/39	Before administration of bismarsen..	320,000	10,600	0.57
7/ 8/39	Before administration of bismarsen..	360,000	10,800	1.07
7/10/39	Before administration of bismarsen..	340,000	11,400	1.20
7/12/39	Before administration of bismarsen..	350,000	12,500	1.01
	15 minutes after.....	240,000	5,850	....
	30 minutes after.....	80,000	6,100	....
	60 minutes after.....	60,000	8,400	....
	2 hours.....	40,000	8,800	....
	5½ hours after.....	50,000	10,900	....
7/13/39	24 hours after.....	60,000	9,100	0.66
7/14/39	2 days after.....	70,000	8,800	0.82
7/15/39	3 days after.....	80,000	9,800	....
7/17/39	5 days after.....	230,000	12,400	0.69
7/21/39	9 days after.....	340,000	7,800	....

* The platelet counts from Dec. 30, 1938 to Jan. 5, 1939 inclusive were made after the administration of 0.1 Gm. of bismarsen, before therapy with ascorbic acid; the counts from July 12 to 21 inclusive were made after the administration of 0.075 Gm. of bismarsen, after therapy with ascorbic acid.

part of the chest and the upper and lower extremities. In the subcutaneous tissues of the lower extremities there were a few ecchymotic areas, the largest being 3 by 5 cm. in size. In the mucous membranes of the soft palate a hemorrhagic bleb was present, 0.5 cm. in diameter. Nasal bleeding continued through July 14. On this date the purpuric lesions were large and distinct; several over the shoulders and the upper part of the chest were 0.5 cm. in diameter. This type of large, round, almost pure black purpuric lesion has been noted by us previously, particularly in connection with bismarsen sensitivity (fig. 3). The platelet counts dropped rapidly after the injection; at the end of thirty minutes the count had fallen from 350,000 before the dose of bismarsen to 80,000 and at the one hour period still further, to 40,000 per cubic millimeter. The platelet count was slow in rising (table 3). On July 15 the patient received 1 cc. of Lederle's concentrated liver extract, and on July 17 the number of platelets had increased from 80,000 to 230,000.

Comment.—This was the only patient of the series sensitive to bismarsen and not to neoarsphenamine. She showed no sensitiveness to mapharsen. The experiment began about seven months after the last administration of bismarsen, but on Feb. 20, 1939 she had experienced a severe reaction, with collapse and purpura haemorrhagica, from an intravenous injection of 0.1 Gm. of sulfarsphenamine. The level of vitamin C in the plasma was up to normal (0.63 mg.) at the beginning of therapy with ascorbic acid. On July 21, the date of the administration of 0.075 Gm. of bismarsen, the vitamin C content of the plasma was 1.01 mg. The toxic reaction was more marked than her previous reaction to 0.1 Gm. of bismarsen on Dec. 30, 1938. The purpuric lesions are well shown in figure 2.

Fig. 3 (case 3).—Large purpuric lesions the occurrence of which followed injection of 0.075 Gm. of bismarsen, after therapy with ascorbic acid, the vitamin C content of the plasma being 1.20 mg. per hundred cubic centimeters.

CASE 4.—B. P., a Negress aged 30, was known to be sensitive to bismarsen and to neoarsphenamine. She became sensitive to bismarsen after fifty-three intramuscular injections. Just when she became sensitive to neoarsphenamine is not known, but the first reaction of which we have any record occurred on Oct. 18, 1938, one month after discharge from the hospital where she had been under observation for five days on account of hemorrhage following the administration of bismarsen.

This reaction to neoarsphenamine, on October 8, followed the injection of 0.1 Gm. of the drug, given intravenously. There were no subjective symptoms following administration, but there was a rapid drop in the platelet count from 380,000 before injection to 65,000 at the end of one hour, at which time purpuric lesions had appeared over the arms and lower extremities. At the end of four hours after injection the platelet count had dropped to 40,000. By the third day after the injection of neoarsphenamine, the number of platelets increased to 270,000 per cubic millimeter.

On June 26, 1939 we began further sensitivity studies on this patient. She gave the following interval history: While she was in the hospital during September 1938, it was learned that she was a morphine addict of long standing. After her discharge and up to the present, it had been increasingly difficult for her to obtain morphine. Recently she had been using an impure product of whole opium, injecting it beneath the skin. In addition to forming subcutaneous abscesses, this substance caused nausea, vomiting and anorexia, and for the past three or four months she had eaten chiefly carbohydrates, when she had been able to eat at all. As a result, the vitamin C content of her diet was considered to be entirely inadequate, an assumption supported by her low plasma content of vitamin C (table 4). While in the hospital in September 1938, she received 900 mg. of ascorbic acid intravenously during forty-eight hours as a therapeutic measure for control of hemorrhage. The vitamin C content in the plasma at the end of that time was 0.42 mg. per hundred cubic centimeters. We cannot judge as to the value of this therapy as we have no control observations.

On June 27 the vitamin C content in the plasma was 0.22 mg. per hundred cubic centimeter of blood; on June 30 it was 0.17 mg. At 10 a. m. on this date she was given 0.1 Gm. of neoarsphenamine, intravenously. Before administration of neoarsphenamine, the platelet count was 450,000; one-half hour after injection, 290,000; one hour after injection, 170,000; at two hours, 210,000, and after twenty-four hours, 260,000. There was no apparent toxic reaction after administration of the drug.

On July 6 the vitamin C content of the plasma was 0.25 mg. per hundred cubic centimeters; the platelet count was 250,000. At this time 0.3 Gm. of neoarsphenamine was administered intravenously. No toxic reaction occurred, but the blood pressure, which had been 120 systolic and 90 diastolic before administration of the drug, dropped to 85 systolic and 60 diastolic one-half hour after. The platelet count fell to 120,000 in fifteen minutes and to 100,000 at the end of one hour. As the patient had been without food all day and had a severe headache, she took a light repast with two cups of coffee about one and one-half hours after the injection. At the end of two hours the platelet count had risen to 120,000 per cubic millimeter. On the following day, twenty-four hours later, the platelet count was 20,000. There were a few small petechiae over the left lower extremity and over the upper anterior part of the chest on the left. The Dalldorf capillary fragility test showed: at —15 cm. pressure, a shower of petechiae; at —10 cm. pressure, eight to ten petechiae. The platelet count returned to normal in five days.

On July 8 the vitamin C content in the plasma was 0.25 mg. per hundred cubic centimeters, and oral administration of 1 tablet of ascorbic acid, 25 mg., was started four times daily. On July 11, 400 mg. intravenously was added every second day up to July 19. The patient received 1,100 mg. by mouth and 2,000 mg. intravenously up to July 19, on which day 0.075 Gm. of neoarsphenamine was given by vein. The vitamin C content of the plasma had increased to 1.01 mg. by July 17, and to 1.5 mg. by July 19. The blood pressure was 125 systolic and 90 diastolic before injection, and the platelet count was 350,000. Fifteen minutes after injection the platelet count was 120,000; at the end of thirty minutes the count was 50,000 platelets per cubic millimeter. The Dalldorf capillary fragility test at this time was: at —15 cm. pressure, 4 to 5 petechiae; at —10 cm. pressure, none. Thirty minutes after the drug had been given the blood pressure was 80 systolic and 64 diastolic. At this time the patient felt weak and took a small amount of food, with a cup of coffee. One hour after injection the platelet count had risen to 105,000 per cubic millimeter. At the end of two hours the platelet

count was 50,000, and a small amount of bleeding from the nasal mucosa was present. During the evening of July 19 there was profuse uterine bleeding, nasal hemorrhage and bleeding from the gums. On the following morning there was much prostration; bleeding continued; the entire body was covered with a purpuric eruption, and several large ecchymotic areas were present. She was therefore admitted to the hospital. The platelet count at this time was 25,000, and the

TABLE 4.—*Data in Case 4*

Date	Time	Platelet Count*	White Cell Count	Plasma Vitamin C Content, Mg. per 100 Cc. of Blood
10/18/38	Before administration of neoarsphenamine	380,000	9,800	....
	15 minutes after	200,000	8,900	....
	30 minutes after	110,000	8,500	....
	60 minutes after	65,000	8,600	....
	2 hours after	48,000	8,700	....
10/19/38	4 hours after	40,000	8,800	....
	24 hours after	100,000	9,100	....
10/20/38	2 days after	270,000	8,900	....
10/25/38	7 days after	340,000	9,000	....
6/27/39	Before administration of neoarsphenamine	250,000	6,500	0.22
6/30/39	Before administration of neoarsphenamine	430,000	7,000	0.17
	15 minutes after	430,000	7,200	....
	30 minutes after	290,000	8,100	....
	60 minutes after	170,000	8,000	....
	2 hours after	210,000	7,700	....
7/ 1/39	24 hours after	260,000	9,100	0.17
7/ 6/39	Before administration of neoarsphenamine	250,000	11,200	0.25
	15 minutes after	120,000	9,700	....
	30 minutes after	120,000	9,400	....
	60 minutes after	100,000	9,500	....
	2 hours after	120,000	10,100	....
7/ 7/39	24 hours after	20,000	6,550	0.25
7/ 8/39	2 days after	70,000	6,750	0.25
7/11/39	5 days after	390,000	7,100	0.31
7/19/39	Before administration of neoarsphenamine	330,000	10,000	1.51
	15 minutes after	120,000	8,300	....
	30 minutes after	50,000	12,200	....
	60 minutes after	105,000	13,400	....
	2 hours after	50,000	11,900	....
	3 hours after	40,000	9,800	....
7/20/39	24 hours after	25,000	9,900	1.13
	32 hours after	40,000	8,600	....
7/21/39	48 hours after	40,000	10,400	1.20
	56 hours after	60,000	8,900	....
7/22/39	3 days after	80,000	8,300	1.20
7/24/39	5 days after	480,000	7,400	0.88

* The platelet counts from Oct. 18 to 25, 1938 inclusive were made after the administration of 0.1 Gm. of neoarsphenamine, before therapy with ascorbic acid; the counts from June 30 to July 1, 1939 inclusive were made after the administration of 0.1 Gm. of neoarsphenamine, before therapy with ascorbic acid; the counts from July 6 to 11, 1939 inclusive were made after the administration of 0.3 Gm. of neoarsphenamine, before therapy with ascorbic acid; the counts from July 19 to 24, 1939 inclusive were made after the administration of 0.075 Gm. of neoarsphenamine, after therapy with ascorbic acid.

bleeding time was twenty-four minutes (Duke), with a nonretractile clot. Marked prostration was present. The blood pressure at 3 p. m. on July 20 registered 100 systolic and 66 diastolic. Just before neoarsphenamine was administered on July 19, 400 mg. of ascorbic acid was administered intramuscularly; this ended the therapy with ascorbic acid. On July 20 the vitamin C content in the plasma was 1.13 mg., a drop of 0.38 mg. in twenty-four hours. When one considers the fact that she had received 400 mg. intramuscularly on July 19, this appeared to be a significant fall. Also, the drop in the hemoglobin content and red blood cell content during the four days which followed the injection of neoarsphenamine

was striking. The red cell count fell from 4,560,000 to 4,010,000 and the hemoglobin content from 12.6 Gm. (92 per cent) to 10.4 Gm. (76 per cent). The patient was discharged from the hospital on July 22.

Comment.—This experiment is the most interesting of the series, in that we were fortunate in securing a patient who was known to be sensitive to neoarsphenamine, whose vitamin C intake was inadequate and who showed a low vitamin C level in the blood (from 0.17 to 0.31 mg.), figures which ordinarily cause one to suspect some clinical signs of vitamin C deficiency. In this connection it should be noted that the Dalldorf capillary fragility tests did not give the readings usually associated with vitamin C deficiency. This might be explained by the fact that the skin of both arms had been the site of trauma and irritation for many years, from self-administered hypodermics, thereby the capillaries were made unusually resistant. This patient has never exhibited any symptoms of a toxic reaction following administration of neoarsphenamine; hence the effects on the platelet count and the hemorrhagic manifestations are the factors to use in judging the degree of her sensitivity to the drug.

The intravenous injection of 0.1 Gm. of neoarsphenamine, Oct. 18, 1938, occurred exactly one month after the patient's discharge from the hospital where she had been treated for hemorrhagic phenomena (when she was given 0.2 Gm. of bismarsen as part of her therapy for syphilis). During hospitalization she received 900 mg. of ascorbic acid intravenously for treatment of the purpura. After one month, one would not expect this vitamin C to be still present in her system, nor did it appear to have influenced her sensitivity to neoarsphenamine, as the injection of 0.1 Gm. of this drug on Oct. 18, 1938 caused a marked diminution of the platelet count from 380,000 to 40,000 in four hours, with a purpuric eruption over the anterior part of the chest and the upper and lower extremities. Nine months later a similar dose of neoarsphenamine produced only a moderate drop in the platelet count (table 4), with no purpuric eruption, in the presence of a vitamin C level in the plasma of 0.17 mg. per hundred cubic centimeters of blood. This is evidence that she had lost much of her sensitivity during the nine months since the previous injection of neoarsphenamine. The intravenous injection of 0.3 Gm. of neoarsphenamine, six days later, produced a marked drop in the platelet count, from 250,000 to 20,000 in twenty-four hours, with a few purpuric lesions. This dose appeared to sensitize her to such an extent that, in spite of a high plasma vitamin C level of 1.51 mg. she had a marked hemorrhagic reaction on being given 0.075 Gm. of neoarsphenamine, a reaction more severe and prostrating than the reaction which sent her to the hospital after she was given 0.2 Gm. of bismarsen on Sept. 14, 1938.

Case 5.—M. M., a man of 66, was sensitive to neoarsphenamine and bismarsen. On Oct. 21, 1937, he received 0.015 Gm. of neoarsphenamine intravenously, with an immediate reaction characterized by cyanosis, rapid feeble pulse, nausea and pros-

tration. He complained of feeling as if he was going to faint. The drop in the platelet count is shown in table 5. At the end of thirty minutes after the injection the platelet count was 80,000; and at the end of two hours petechiae began to appear over the neck, the upper anterior part of the chest and the upper and lower extremities. At this time he was seized by a chill for which a subcutaneous injection was given of 1 cc. of epinephrine (1:1,000). The epinephrine caused a temporary rise in the platelet count (table 5). Prostration was so severe that we sent the patient into the hospital for observation over a twenty-four hour period. Recovery was rapid; by October 25 the platelet count had returned to a level of 300,000 per cubic millimeter.

On Jan. 2, 1938 the patient began to take 3 tablets of ascorbic acid daily, each tablet containing 100 mg. On January 6 he took only 1 tablet, but received 200 mg. of ascorbic acid intravenously. The second dose of 100 mg. was administered five minutes before he received an intravenous injection of 0.005 Gm. of

TABLE 5.—*Data in Case 5*

Date	Time	Platelet Count*	White Cell Count
10/21/37	Before administration of neoarsphenamine	580,000	12,400
	15 minutes after	250,000	11,000
	30 minutes after	80,000	8,500
	60 minutes after	150,000	10,100
	2 hours after	170,000	13,900
	3 hours after	110,000	21,100
	7 hours after	190,000	14,800
10/22/37	24 hours after	100,000	12,600
10/23/37	2 days after	130,000	8,000
10/25/37	4 days after	300,000	11,200
10/26/37	5 days after	450,000	12,400
1/ 6/38	Before administration of neoarsphenamine	540,000	14,500
	15 minutes after	130,000	13,400
	45 minutes after	90,000	12,000
	60 minutes after	115,000	11,300
	1½ hours after	80,000	12,300
	5 hours after	55,000	36,000
1/ 7/38	24 hours after	190,000	17,400
	30 hours after	210,000	14,900
1/ 8/38	2 days after	320,000	14,100
1/13/38	7 days after	380,000	13,800

* The platelet counts from Oct. 21 to 26, 1937 inclusive were made after the administration of 0.015 Gm. of neoarsphenamine, before therapy with ascorbic acid; the counts from Jan. 6 to 13, 1938 inclusive were made after the administration of 0.006 Gm. of neoarsphenamine, after five days' therapy with ascorbic acid.

neoarsphenamine. Although this dose of the arsenical was only one third of the amount administered on Oct. 21, 1937, the injection was scarcely completed before cyanosis, nausea, headache and rapid pulse developed. Forty-five minutes after the onset of the reaction, a severe chill came on, for which 1 cc. of epinephrine (1:1,000) was given subcutaneously. The platelet count rose from 90,000 to 115,000 after the administration of the epinephrine at the one hour period after the administration of neoarsphenamine. At the end of five hours the platelet count had dropped to 55,000, and purpuric lesions were appearing over the neck, the shoulders, the upper part of the chest and the extremities. On account of severe prostration and the patient's senility, he was sent to the hospital for a period of twenty-four hours. He recovered rapidly; by January 8, three days after he had received the neoarsphenamine, the platelet count was 320,000 per cubic millimeter.

CASE 6.—S. H., a Mexican woman aged 45, had nausea, vomiting and headache after administration of 0.2 Gm. of neoarsphenamine on Nov. 20, 1937. On the following day purpura appeared over the arms, the upper anterior part

of the chest and both lower extremities. On December 3, 0.1 Gm. of neoarsphenamine was administered intravenously for experimental production of thrombopenic purpura and to test her sensitivity to the arsenicals. An immediate reaction occurred, characterized by nausea, vomiting, rapid pulse, cold extremities and headache. The platelet count dropped to 80,000 at the end of thirty minutes after the injection, but rose again gradually, so that at the end of the two hour interval the count was 190,000 per cubic millimeter (table 6). On December 7 the platelet count was 240,000 per cubic millimeter, and the patient seemed to have recovered from her reaction.

On December 23 the patient was started on a regimen including daily oral dosage of 1 tablet of ascorbic acid, each tablet containing 100 mg. From December 29 to January 5 this intake of ascorbic acid was supplemented by daily intravenous injections of 100 mg. of ascorbic acid. On January 5 the dose of 100 mg. of ascorbic acid was injected intravenously; and, with the needle left in situ, a

TABLE 6.—*Data in Case 6*

Date	Time	Platelet Count*	White Cell Count
12/3/37	Before administration of neoarsphenamine	270,000	8,500
	15 minutes after	160,000	6,200
	30 minutes after	80,000	7,600
	60 minutes after	130,000	8,100
	2 hours after	190,000	9,150
12/4/37	24 hours after	70,000	11,200
12/6/37	3 days after	140,000	9,800
12/7/37	4 days after	240,000	11,400
12/8/37	5 days after	270,000	10,300
1/ 5/38	Before administration of neoarsphenamine	360,000	10,200
	15 minutes after	240,000	7,100
	60 minutes after	70,000	6,200
	1½ hours after	80,000	7,050
	2 hours after	70,000	7,350
1/6/38	24 hours after	110,000	7,500
1/8/38	3 days after	300,000	10,000

* The platelet counts from Dec. 3 to 8, 1937 inclusive were made after the administration of 0.1 Gm. of neoarsphenamine, before therapy with ascorbic acid; the counts from Jan. 5 to 8, 1938 inclusive were made after the administration of 0.075 Gm. of neoarsphenamine, after fourteen days' therapy with ascorbic acid.

syringe was attached and 0.075 Gm. of neoarsphenamine was administered immediately after the ascorbic acid. The reaction of the neoarsphenamine consisted of nausea, vomiting, rapid pulse, severe headache and prostration, and these symptoms began before all of the solution had entered the vein. One hour after the injection, the platelet count had dropped to 70,000 from 360,000 per cubic millimeter (table 6). At the end of two hours the bleeding time (Duke) was thirty minutes, and a purpuric eruption was becoming evident over the lower extremities. Twenty-four hours later the platelet count was 110,000. On January 8 the platelet count was 300,000. The patient felt somewhat weak, and purpuric lesions had spread to the neck, the shoulders, the arms, the upper part of the chest and the lower extremities. Clinically, the patient had recovered from the injection, but the purpuric eruption faded slowly.

Comment (cases 5 and 6).—Cases 5 and 6 can be commented on together, as the experiment in each instance was designed to test the hypothesis advanced by certain investigators, particularly by Giroud and Giroud,[22] who reported that intravenous administration of 100 mg.

22. Giroud, P., and Giroud, A.: Influence du régime alimentaire sur la sensibilité du lapin à la séro-anaphylaxie, Compt. rend. Soc. de biol. **122**:537, 1936.

of vitamin C to rabbits one-half minute to five minutes before the shocking dose of antigen gave almost complete protection against anaphylactic shock. In both cases 5 and 6 vitamin C was given for a few days previous to administering the dose, and from one-half minute to five minutes before administering the dose of neoarsphenamine. There was no diminution in the shock symptoms of these patients and no particular lessening of the degree of platelet drop and purpuric phenomena after vitamin C therapy, as compared with previous reactions which occurred when no preliminary vitamin C therapy had been instituted, and in each case smaller doses of neoarsphenamine were administered after vitamin therapy.

TABLE 7.—*Data in Case 7*

Date	Time	Platelet Count*	White Cell Count	Plasma Vitamin C Content, Mg. per 100 Cc. of Blood
12/27/37	Before administration of neoarsphenamine	420,000	9,800	....
12/28/37	Before administration of neoarsphenamine	.....	.....	0.81
12/29/37	Before administration of neoarsphenamine	.....	.....	0.84
12/30/37	Before administration of neoarsphenamine	460,000	5,600	....
	15 minutes after	410,000	9,100	....
	30 minutes after	490,000	9,100	....
	60 minutes after	470,000	6,700	....
	1½ hours after	430,000	7,200	....
12/31/37	24 hours after	390,000	9,600	....
1/ 3/38	Before administration of neoarsphenamine	340,000	11,300	....
	15 minutes after	380,000	11,500	....
	30 minutes after	330,000	11,900	....
	60 minutes after	300,000	11,950	....
		330,000	12,700	....
8/ 2/39	Before administration of neoarsphenamine	290,000	11,100	....
	15 minutes after	230,000	4,900	....
	30 minutes after	150,000	5,100	....
	60 minutes after	100,000	4,100	....
8/ 3/39	24 hours after	200,000	9,300	....

* The platelet counts for Dec. 30 and 31, 1937 were made after the administration of 0.1 Gm. of neoarsphenamine, after therapy with vitamin C; the counts for Jan. 3, 1938 were made after the administration of 0.05 Gm. of neoarsphenamine, after therapy with vitamin C; the counts for Aug. 2 and 3, 1939 were made after the administration of 0.1 Gm. of neoarsphenamine, with no vitamin C therapy.

CASE 7.—J. L., an Italian aged 45, was 1 of 3 patients with thrombopenic purpura following neoarsphenamine therapy reported by us in 1936.[21] He was hospitalized on Dec. 27, 1937, so that the effects of vitamin C on his sensitivity to neoarsphenamine might be studied. The plan was to administer a dose of 0.1 Gm. of neoarsphenamine to test his present sensitivity, then to administer vitamin C intravenously for about one week in an attempt to saturate the tissues. After one day in the hospital he informed us that he would not remain longer than December 31. On account of this short period for observation, no neoarsphenamine was administered until after the patient had received 300 mg. of ascorbic acid intravenously. On December 30, 0.1 mg. of neoarsphenamine was given intravenously, with the result that no untoward symptoms occurred after the dose and no significant decrease in the platelet counts took place (table 7). This was surprising, as he had previously been very sensitive to neoarsphenamine. The last dose received was on March 3, 1935. On Jan. 3, 1938, after five days of no vitamin C intake except in his diet, the patient received a second dose of neoarsphenamine, 0.05 Gm. No reaction occurred and no purpura (table 7).

The number of platelets decreased only slightly. On Aug. 2, 1939, after long search for this patient, he was located and induced to return for further testing relative to his sensitivity to neoarsphenamine. On this date he received 0.1 Gm. of neoarsphenamine intravenously. There was no immediate reaction. After about one hour he had a chill and slight nausea. On the following day he felt normal. The platelet count fell considerably, but no purpuric lesions occurred (table 7). There had been no special vitamin C intake between the dates of Dec. 30, 1937 and Aug. 2, 1939, except that incidental to his diet.

Comment.—This experiment is one of the most instructive and important of the series, for it shows how data may be misleading when the experiment is incomplete. Had we given only the two injections of neoarsphenamine, on Dec. 30, 1937 and on Jan. 3, 1938, we might have interpreted this patient's lack of a sensitivity reaction in each instance to the protective influence of the vitamin C. The mild reaction with no purpuric lesions on Aug. 2, 1939 shows that he had experienced a loss of sensitivity to neoarsphenamine in the interval from March 3, 1935 to Dec. 31, 1937. The two injections of neoarsphenamine, on Dec. 31, 1937, and on Jan. 3, 1938, served to increase his sensitivity to such an extent that it was still present on Aug. 2, 1939, but much less in degree as compared with the reaction of March 3, 1935, when he had a prompt toxic reaction with purpura after the administration of 0.1 Gm. of neoarsphenamine.

SUMMARY AND CONCLUSIONS

Attacks of experimental thrombopenic purpura following the administration of neoarsphenamine and bismarsen were repeatedly reproduced in 7 patients who were sensitive to one or the other or to both of these preparations.

Vitamin C in crystalline form as ascorbic acid, administered parenterally, orally and ingested in the diet, was given in varying amounts to these 7 patients, to determine whether it modified their sensitivity to the arsenicals or inhibited the occurrence of thrombopenic purpura following the administration of the arsenical responsible for their sensitivity.

It was found impossible to standardize the sensitivity reaction to a given amount of the arsphenamine preparation causing a reaction. The variation of the reaction to different amounts of the drug was marked in the same patient at various time intervals. Variation in the different patients of the series was considerable and appeared as a distinctly individual characteristic. At no time and in no patient observed was there any appreciable modification of sensitivity reaction during or after administration of vitamin C. The apparent increase in severity of the reactions after administration of vitamin C in certain of these patients was probably due entirely to increased sensitivity as the result of previously administered arsphenamine.

DERMATOMYOSITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS

II. A COMPARATIVE STUDY OF THE ESSENTIAL CLINICOPATHOLOGIC FEATURES

HARRY KEIL, M.D.
Associate Dermatologist, Beth David Hospital
NEW YORK

In a previous publication an attempt was made to correlate the dermatologic and internal medical manifestations presented by a group of 5 cases illustrating what might be termed a "transitional" state between dermatomyositis and systemic lupus erythematosus.[1] With but one exception, the cases were observed by me over relatively long periods, while the remaining instance provided an opportunity to furnish additional data on the early phases of the condition. Besides these, other examples of dermatomyositis that have come under my observation were mentioned briefly in connection with the elaboration of certain fundamental points. It is my belief that these diseases or manifestations of them will "become more common" when the practitioner learns to recognize them and their atypical variants; this is already apparent in the case of systemic lupus erythematosus. It is interesting that the literature now contains the reports of hundreds of instances of dermatomyositis, many of these having been recorded under a variety of titles. Though these diseases may, at times, present rather superficial resemblances to "rheumatism," they are unrelated to rheumatic fever in the precise sense in which that disease is understood today, and a vast number of postmortem observations appear to substantiate this view.

Apart from the cases of "transitional" conditions, there are many other instances in which it is difficult, on clinical grounds at least, to differentiate systemic lupus erythematosus from dermatomyositis, especially when the patient is seen either very early in the course or in the later stages of the disease. There are rare examples of the former condition that apparently fulfil all the clinicopathologic criteria for diagnosis and in which more or less marked involvement of the muscles is present; contrariwise, there are instances of the latter disease in which there are cutaneous manifestations that are differentiated with difficulty, if at all, from those associated with systemic lupus erythematosus. Detailed

1. Keil, H.: Dermatomyositis and Systemic Lupus Erythematosus: I. A Clinical Report of "Transitional" Cases, with a Consideration of Lead as a Possible Etiologic Factor, Arch. Int. Med. **66**:109 (July) 1940.

studies of these syndromes reveal, however, that the average typical example of each disease ordinarily pursues a different course and in each individually peculiar internal medical features and fairly distinctive cutaneous lesions are present. Nevertheless, a considerable amount of overlapping does occur, as indicated in the case protocols previously detailed [1] as well as in others in the literature. Yet, there is, to borrow the words of Osler, "a positive advantage in recognizing the affinities and the strong points of similarity in affections usually grouped as separate diseases."

Among the clinical phenomena that may be encountered in both conditions are fever, pains of presumably articular nature, similar cutaneous and oral lesions, sensitivity to sunlight, Raynaud-like symptoms, lymphadenopathy, splenomegaly, leukopenia, a tendency to purpura, alopecia of the scalp, sterile cultures of blood, muscular involvement and renal disease. Both diseases may also run an afebrile course, and at times the clinical picture may be dominated by what may be called the sequelae of these conditions. Despite the apparent close similarities in features, these diseases may be differentiated if one pays close attention to certain clinical refinements. While these differences appear to warrant separation of the syndromes, it must be stressed again that the considerable overlapping of features suggests a closer relation between these conditions than has been generally accepted.

A. CLINICAL DATA

1. *Age, Sex and Seasonal Incidence.*—Systemic lupus erythematosus shows a striking predilection for young women, who often manifest unusual hypersensitivity to sunlight, but men may also be affected by this disease. Likewise, instances are encountered in children as well as in persons in the older age groups. Nevertheless, the vast majority of cases occur in young women, and, as the prognosis is poor, few of the patients seem to reach a mature age. The old dictum that lupus erythematosus does not occur in persons in the fifth decade and beyond because persons who would have had the disease then have already died from pulmonary tuberculosis cannot be substantiated by postmortem studies.[2] Of the two diseases, dermatomyositis is the more likely to occur in the male sex and appears, also, to be more common in older persons. There are, however, numerous instances in all age groups and in both sexes, so that a differential diagnosis based on these factors is hazardous. Likewise, the peculiarity of sensitivity to sunlight has been

2. Keil, H.: (*a*) Relationship Between Lupus Erythematosus and Tuberculosis: A Critical Review Based on Observations at Necropsy, Arch. Dermat. & Syph. **28**:765 (Dec.) 1933; (*b*) Conception of Lupus Erythematosus and Its Morphologic Variants, with Particular Reference to "Systemic" Lupus Erythematosus, ibid. **36**:729 (Oct.) 1937.

recorded as occurring in many instances of dermatomyositis.[3] As a corollary, both conditions are apt to have their clinical onset or exacerbation of symptoms between late spring and early autumn, though there are exceptions to this rule. The statement is often made that dermatomyositis is more likely to occur during the winter, but the records in the literature, when carefully analyzed, as well as my own observations, are at variance with this hypothesis. It is, however, true that in both conditions certain vasomotor phenomena, such as the Raynaud-like symptoms, may become particularly conspicuous with the advent of cold weather. This observation does not contradict the main thesis, for the vasculature in these patients may react to a variety of factors which, in view of the present state of knowledge, are to be regarded as predisposing agents rather than as the actual cause of the malady. Thus, I have observed several examples of superficial disseminated lupus erythematosus in which the illness had its apparent onset after exposure to sunlight or in which the patient was aware of previous sensitivity to this factor, yet in which subsequent exacerbations occasionally occurred during the cold weather.

2. *Cutaneous Lesions.*—This subject will be discussed more fully in a succeeding publication. Here it is my intention, subject to the limitations previously stated, to mention some of the differential clinical points that tend to favor the diagnosis of dermatomyositis. These are: (1) the early or initial involvement of the eyelids by a peculiar type of erythematous and telangiectatic edema; (2) the occurrence of special atrophic areas (soft and hard) over the small articulations of the fingers, occasionally about the larger joints and sometimes on the trunk; (3) the appearance of large areas of noncircumscribed erythema in relation to large masses of simultaneously affected muscles and subcutaneous tissue; (4) the occasional occurrence of an unusual degree of hypertrichosis, generally on areas the sites of previously inflamed subjacent structures; (5) the appearance of peculiar whitish areas in such places as the oral mucosa and the tongue, and (6) periungual and other changes.

As in the case of systemic lupus erythematosus,[2b] there is often no precise correlation in dermatomyositis between the extent and intensity of the cutaneous lesions and the degree of muscular or internal visceral involvement. It is common to observe instances of both diseases in

3. (*a*) Turner, J. C.: Dermatomyositis: A Study of Three Cases, New England J. Med. **216**:158, 1937. (*b*) Schuermann, H.: Zur Klinik und Pathogenese der Dermatomyositis (Polymyositis), Arch. f. Dermat. u. Syph. **178**: 414, 1939. (*c*) Dowling, G. B.: Dermatomyositis, St. Thomas Hosp. Rep. **1**: 150, 1936. (*d*) Towle, H. P.: Dermatomyositis, Arch. Dermat. & Syph. **34**: 298 (Aug.) 1936. (*e*) Witts, L. J.: A Case of Dermatomyositis, Brit. J. Dermat. **48**:509, 1936. (*f*) Wanderer, E.: Dermatomyositis, Zentralbl. f. Haut- u. Geschlechtskr. **53**:145, 1936. (*g*) Keil, H.: Unpublished data.

which the manifestations in the skin may be overlooked or their significance underestimated, especially in cases in which mild changes appear. Contrariwise, there are occasional examples of both diseases, or allied syndromes, in which the cutaneous lesions either are apparently absent or occur relatively late in the course. Under such circumstances the diagnostic difficulties are enhanced, but there is considerable evidence that these cases are intimately related to those in which there is a striking eruption at the onset. In the past there has been much controversy regarding the classification of the condition in these instances, but detailed clinicopathologic studies have aided, at least in the case of systemic lupus erythematosus, in the formulation of criteria permitting recognition of instances of certain obscure syndromes temporarily or permanently deprived of the "revealing" cutaneous lesions. Among these may be mentioned:

1. Cases of so-called rheumatoid arthritis in which there is sensitivity to sunlight, with subsequent or simultaneous involvement of the kidneys, the serous membranes and other parts.[2b]

2. Cases of febrile thrombopenic purpura in which the cultures of blood are sterile and in which there occurs involvement of such organs as the kidneys. In a previous publication [4] I recorded the protocols of 2 such instances in which successful splenectomies for thrombopenic purpura were performed and in which the clinical picture of systemic lupus erythematosus subsequently appeared. Recently, a third example of the syndrome has come under my observation, and several other investigators have written to me regarding additional instances.

3. Peculiar examples of polyserositis with widespread involvement of other systems, including the renal tissue. This polyserositic form of systemic lupus erythematosus has been described by a number of observers, including Tremaine,[5] Christian [6] and Friedberg, Gross and Wal-

4. Keil, H.: Relation Between "Systemic" Lupus Erythematosus and a Peculiar Form of Thrombocytopenic Purpura, Brit. J. Dermat. **49**:221, 1937. The original draft of this paper was perused by both G. Baehr and P. Klemperer among others in 1933. At that time Baehr added annotations in which he claimed credit with Keil for knowledge of the capillary lesions in the syndrome described for the first time in this paper, and he excluded, intentionally and completely, the names of P. Klemperer and A. Schifrin. I did not include these annotations in the paper published in 1937. While Klemperer was not the first to discover the vascular lesions in the glomerular capillaries, especially in their relation to systemic lupus erythematosus, I feel that he deserves great credit for the descriptive name "wire-loop" lesions, used to describe these alterations in the kidneys.

5. Tremaine, M. J.: Subacute Pick's Disease (Polyserositis) with Polyarthritis and Glomerulo-Nephritis: A Report of Two Fatal Cases, New England J. Med. **211**:754, 1934.

6. Christian, H. A.: Long-Continued Fever with Inflammatory Changes in Serous and Synovial Membranes and Eventual Glomerulonephritis: A Clinical Syndrome of Unknown Etiology, M. Clin. North America **18**:1023, 1935.

lach [7] among others, and I have had the opportunity of studying such instances, occurring with or without the appearance of the rash of lupus erythematosus. Examples of this syndrome in males have also come under my observation.

Just as the term systemic lupus erythematosus usually implies the simultaneous appearance of a typical rash, so the designation of dermatomyositis is generally reserved for instances in which there is implication of both skin and muscle. As in the case of the former disease, cutaneous manifestations may apparently be lacking in instances of dermatomyositis, if not permanently, at least temporarily, and here again there has arisen considerable debate regarding classification. When the rash is absent it is my custom to designate such examples as polymyositis (of such types as pure, hemorrhagic, fibrotic and calcific); there is considerable evidence indicating an alliance between many cases of these forms of disease and cases of ordinary dermatomyositis. Finally, there are a few other names that are occasionally met with in studying this disease, and it is proposed to complete this section by defining these terms:

1. Dermatomucomyositis. The oral lesions are emphasized by this term.

2. Dermatoneuromyositis. This name stresses the occasional secondary element of involvement of the small nerves situated in relation to the muscular bundles.

3. Angiomyositis. Originally this term referred to capillary dilatation as the presumable primary event in this disease. It has been used also in relation to the myopathies observed in the wake of arterial or venous disease of various types.

4. Poikilodermatomyositis. This name designates a form of dermatomyositis in which there occurs a reticulated type of pigmentation and in which muscular atrophy generally, but not always, appears in an insidious and often painless manner. The course is usually more chronic. These attributes are, however, inadequate to differentiate poikilodermatomyositis from ordinary dermatomyositis.

5. Poikiloderma atrophicans vasculare. Under this title numerous examples of poikilodermatomyositis have been recorded; in such instances either muscular disease has been overlooked, its significance depreciated or its clinical appearance much delayed. It is probable that Jacobi's original case [8] of poikiloderma atrophicans vasculare was merely

7. Friedberg, C. K.; Gross, L., and Wallach, K.: Nonbacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions, Arch. Int. Med. **58**:662 (Oct.) 1936.

8. Jacobi, E.: Poikilodermia Atrophicans Vascularis, in Neisser, A., and Jacobi, E.: Ikonographia dermatologica, Berlin, Urban & Schwarzenberg, 1910, p. 95.

an unrecognized case of poikilodermatomyositis (dermatomyositis); the reasons for this view, as well as the entire subject of the poikilodermas, will be discussed in another publication.

6. Myositis fibrosa. This pathologic term refers to a common method of healing in instances of muscular diseases of various types. Some of the cases appear to belong in the category of dermatomyositis, as indicated by my study of the cutaneous manifestations and the general clinical features. This term creates difficulty only when it is used clinically to express the concept of a single disease instead of the pathologic end stage of many conditions, for example, the Jendrassik type of contracture.

7. Scleroderma. Some observers, among them outstanding men like Dowling,[9] have claimed that dermatomyositis is but one of the variants of scleroderma. It is my belief, however, that the resemblances are, on the whole, superficial and that these diseases should be sharply differentiated, despite occasional similarities in the clinicopathologic features.

8. Suppurative polymyositis. This name refers to the frankly purulent or seropurulent forms of polymyositis observed in the course of various types of bacteremia. Confusion with ordinary dermatomyositis is likely only when thin seropurulent fluid is observed on sectioning of the muscles (for example, Str. haemolyticus), but minute anatomic study and culture generally differentiate them with ease. It is universally agreed that these conditions have little in common with dermatomyositis, except for occasional similarities in the clinical picture.

9. Other forms of polymyositis. Involvement of muscles may sometimes be encountered after attacks of true scarlet fever, sinusitis, measles and many other diseases. The entire subject of the myopathies is sorely in need of fresh clinicopathologic studies, especially in regard to the unusual anomalies seen in association with the lymphoblastomas, and it appears that the musculature is affected in association with a larger number of conditions than is commonly suspected. This subject will receive additional consideration in the section concerned with the pathologic anatomy.

Nearly all the terms listed are probably superfluous and, perhaps, even confusing: superfluous, because they tend to stress one feature at the expense of the others; confusing, because they add a multitude of names and syndromes. The term dermatomyositis, while perhaps not inclusive enough, emphasizes the chief diagnostic features of the syndrome, with the proviso that there are other variants and atypical clinical pictures to be included in this disease. Once the clinical picture of this condition is understood, the establishment of the diagnosis is fairly

9. Dowling, G. B.: Two Cases of Dermatomyositis, Proc. Roy. Soc. Med. **31**:1357, 1938.

simple in the average case; only on the basis of such knowledge will it become possible, finally, to circumscribe the conception of the disease.

3. *Disease in the Muscles.*—The following discussion will be restricted chiefly to those instances in which there occurs involvement of the striated musculature, exclusive of the heart.

(*a*) Small Muscles: I have observed involvement of the interosseous and the small muscles of the hands in both systemic lupus erythematosus and dermatomyositis; this phenomenon appears to be more common in the latter disease, and especially in those cases showing a "transitional" state. Some observers believe that only the larger muscular masses in the proximal parts of the limbs are affected in dermatomyositis, but it is a view that admits of many exceptions. Indeed, practically any striated muscle in the body may be implicated in dermatomyositis, especially when the process is severe and widespread. In addition to the involvement of the small muscles in the hands, there is commonly seen in dermatomyositis involvement of the pharyngeal, laryngeal, intercostal, diaphragmatic and ocular muscles among others, and disease in these parts contributes significantly toward the evolution of a distinctive clinical picture. Involvement of these parts is especially important prognostically, as this factor is a direct or indirect cause of death, though it is probable that there may be occasional recoveries. Thus far, I have not encountered any typical example of systemic lupus erythematosus in which these small muscles were affected, at least to an extent sufficient to produce recognizable symptoms.

(*b*) Large Muscles: Dermatomyositis is the disease par excellence in which the large muscular masses are chiefly affected, especially in the limbs. Increased opportunities for minute anatomic studies have led to the knowledge that practically any of the striated muscles may be involved in this disease. When, for example, the masseter muscles are affected, especially with concurrent implication of the subcutaneous tissue, the clinical picture of scleroderma may be closely simulated, and doubtlessly many examples of dermatomyositis have been classified in the category of scleroderma on the basis of such cursory similarities. In the chronic stage, occasionally early in the course, the secondary fibrosis occurring in parts near the joints or even in more remote areas may lead to the formation of contractures; in advanced phases of development the clinical picture is the counterpart of what is commonly described as myositis fibrosa. That in most instances there is excruciating pain on palpation of the muscles and the directly overlying tissues or on active or passive motion of the parts is well known; it is, however, not sufficiently appreciated that the factor of edema, which undoubtedly contributes significantly to the painful element, may be minimal, inconspicuous or altogether absent, and in such instances wasting of the

muscles may proceed in an insidious and often painless manner. In common with other observers, I have encountered in the course of ordinary systemic lupus erythematosus what may be termed "myalgic" phenomena, but I have not yet had the opportunity to submit such areas to the control of a minute anatomic examination. Not all the painful, edematous, reddened, deeply situated masses appearing in the limbs and accompanied by muscular swellings are examples of primary disease in the muscles, for I have seen a phlebitis in the arm of a patient with systemic lupus erythematosus simulate this appearance closely; similar phenomena associated with other conditions have been studied exhaustively by Lorenz and other observers.

In the section devoted to articular manifestations, the probable reason for the confusing of muscular and tendinous involvement with pains in the joints will be discussed. This phenomenon was understood by some observers over fifty years ago, but seems to have been forgotten or, at least, its significance seems to have been underestimated.

Regarding the anatomic changes in biopsy specimens of muscles, there is a great deal of uncertainty as to what alterations are to be considered as significant, especially when these are minimal, and it must be admitted that absolute criteria have not yet been evolved. In every instance, however, the pathologic changes should be interpreted in terms of the clinical features; this is the only way in which it will become possible to evaluate such observations properly. There are many technical difficulties in evaluating the results of such examinations, and the subject of the myopathies needs enlightenment on the basis of more intensive and systematic studies in a variety of conditions, both abnormal and normal.

The evidence for the occasional collateral involvement of the skin and muscles in dermatomyositis will be reviewed in another publication.

4. *Involvement of Subcutaneous Tissue.*—Although dermatomyositis is usually regarded as a disease affecting the muscles chiefly, the subcutaneous tissues are often implicated to a remarkable degree. In all likelihood, involvement of this structure contributes, partly at least, to the marked and often rapid wasting of many patients as well as to the doughy, firm, almost boardlike infiltrations regarded, when present, as characteristic of the disease. Whether the subcutaneous tissue is affected by direct continuity from the process in the muscles or whether the two areas are simultaneously involved by the same process is a question which cannot as yet be answered precisely. The histologic changes in the subcutaneous fat will not be discussed here, except for the statement that the vascular lesions and the *Wucheratrophie* encountered in many cases are probably not pathognomonic of a single disease. Systemic lupus erythematosus is usually free from such involve-

ment, except possibly in a few instances, but this conclusion cannot be stated confidently, for few studies have been concerned with this tissue. Tremaine [5] and others, including myself, have observed instances in which there was a rapid loss of weight, often disproportionate to the severity of the clinical features, but the exact nature of this phenomenon has not been determined, and it is probable that in systemic lupus erythematosus there are numerous factors accounting for such rapid loss of weight. In both diseases, but especially in dermatomyositis, it is common to encounter deep-seated, more or less transitory, edematous infiltrations in various parts of the body, generally in the subcutaneous tissue and easily differentiated from angioneurotic edema. In the fifth case of the previous report [1] this occurred in the cheeks, the situation and subsequent firmness suggesting scleroderma; the analogies were, however, only superficial. Calcific deposits may occur occasionally in the subcutaneous tissues in association with both conditions, and it appears that these are laid down in areas previously damaged, probably secondary to vascular disease or to the local intense edema of the parts. This phenomenon is also encountered in instances of scleroderma and probably other disease, in which the mechanism seems to be similar. The pathogenesis of these deposits may be contrasted possibly with that in idiopathic universal calcinosis, in which, according to the interesting observations of Bauer and his co-workers,[10] calcium salts are deposited in tissues free from previous damage. Calcification in the muscles may be found occasionally in dermatomyositis, sometimes in cases of other diseases; I have not yet encountered this phenomenon in instances of systemic lupus erythematosus.

5. *Articular Involvement.*—Patients afflicted with systemic lupus erythematosus often complain of pains in the joints. Usually these are of the nature of polyarthralgia, without definite evidence of intra-articular disease. It is probable that pathologic alterations will be found in the synovial membrane and the periarticular tissues, but exhaustive minute anatomic studies at this stage of the disease are lacking. In addition to cases in which this mild type of articular involvement occurs, there are instances of systemic lupus erythematosus in which the clinical findings in the joints seem to simulate early rheumatoid arthritis to such a degree as to render differential diagnosis difficult. In one such example Tremaine [5] observed anatomic evidence of hypertrophy of the synovial villi, formation of subperiosteal bone and an inflammatory reaction in the periarticular tissue. It is not yet certain that the pathologic changes in rheumatoid arthritis are sufficiently distinctive

10. Bauer, W.; Marble, A., and Bennett, G. A.: Further Study in a Case of Calcification of Subcutaneous Tissue ("Calcinosis Universalis") in a Child, Am. J. M. Sc. **182**:237, 1931.

to allow an etiologic classification on that basis. Thus far, I have not encountered cases in which the typical ulnar deviation of more or less advanced rheumatoid arthritis was present, though I have observed several instances in which there were marked periarticular thickenings in the fingers, knees and other parts. As was previously stated, such cases are differentiated from instances of the ordinary type of rheumatoid arthritis by unusual sensitivity to sunlight and ultraviolet rays, renal disease, involvement of various serous membranes, a typical rash and other features, and for patients with such symptoms gold salts should be administered with the utmost circumspection, certainly not in large doses. When the collateral evidence is lacking or, perhaps, overlooked, the early diagnosis of systemic lupus erythematosus is not likely to be made. In my own observations, these cases have always concerned members of the female sex, but it is probable that exceptions will be found. Except rarely, the atrophy in the interosseous muscles and the muscles in the thenar and hypothenar eminences was entirely out of proportion to the severity of the subjective symptoms and the objective signs in the small joints of the hands; in most instances under my observation articular pains were minimal or altogether absent.

Dermatomyositis generally spares the joints, at least in a pathologic sense. There are, however, patients who complain of pains that seem to be about or near the articulations, but it is likely that in such instances the deeper tendons, the terminal portions of the muscles or even the subcutaneous tissues in this general region will be found to be implicated by a vascular, inflammatory or edematous process or by combinations of the three. Over fifty years ago Hepp[11] and others said that they recognized that disease in the tendinous portions of the muscles is often responsible for the pains about the joints, and while there is no abundance of anatomic protocols to prove the point, this seems likely when one considers the clinicopathologic features closely. Such pains may possibly also arise in connection with secondary involvement of the nerve endings in widespread disease of the muscular parenchyma; this phenomenon, the significance of which is difficult to assess, is probably uncommon.[11a] In this respect dermatomyositis seems to contrast with periarteritis nodosa, a disease that may at times show analogous clinical features. In periarteritis nodosa involvement of the nerves, which is generally found to be secondary to disease in the arteries supplying these structures, produces the clinical picture of a true neuritis,

11. Hepp, P.: Ueber Pseudotrichinose, eine besonderer Form von acute parenchymatöser Polymyositis, Berl. klin. Wchnschr. **24**:297, 1887.

11a. In an interesting paper Kellgren (Kellgren, J. H.: Observations on Referred Pain Arising from Muscles, Clin. Sc. **3**:175, 1938) found that pain in the muscles of the limbs is often referred to joints or deeply near joints; hence, true articular pains may be simulated by this mechanism in some instances.

with all the usual accompanying signs, including the reaction of degeneration to the electrical current. The status of cases of so-called intermediary conditions is debatable and will not be discussed here; it may be said, however, that with but rare exceptions the clinical picture of the average example of dermatomyositis is vastly different from that of periarteritis nodosa.

While there is no clinical evidence of genuine involvement of joints in dermatomyositis, there are encountered, on the other hand, articular deformities due to contracture produced by fibrosis of the parts already mentioned. These contractures are generally observed in well established conditions, but occasionally they may occur surprisingly early in the course. In the end stages the clinical picture of myositis fibrosa is produced. The observation of such cases is the basis of my belief that many instances of so-called myositis fibrosa represent merely the terminal phases of chronic dermatomyositis or a related syndrome. This belief is, moreover, bolstered by a study of the cutaneous lesions associated with the disease; for example, Blau's first patient,[12] whom I had the opportunity to observe, showed the typical patches over the small joints of the hands and in the other usual sites. Blau stressed the point that the contractures in his 2 cases of myositis fibrosa were not the result of articular disease, but were rather the sequel of tension in the tendons opposing movements in the joints. As far back as 1888 Jacoby [13] made a similar observation in reporting his case of polymyositis, and many others have emphasized this point, which often seems to be overlooked clinically; on a number of occasions I have seen examples of this disease labeled as rheumatoid arthritis. In cases of dermatomyositis such contractures are observed chiefly about the elbows, knees, hips and fingers. I cannot recall having seen a similar phenomenon in instances of systemic lupus erythematosus aside from a moderate stiffness in the knees and in the finger joints proper, simulating the clinical picture of rheumatoid arthritis closely. In occasional instances of dermatomyositis there may be rarefaction of the bones in the neighborhood of joints as shown by roentgenograms; the precise genesis of this condition is unclear at present.

6. *Renal Disease.*—Systemic lupus erythematosus affects the kidneys in such a high percentage of cases that this feature may be regarded, with considerable justification, as an integral part of the disease. The urinary findings are comparable with those observed in "inflammatory nephritis"; occasionally gross hematuria is present. However, micro-

12. Blau, A.: Primary Generalized Myositis Fibrosa: Report of Two Cases with Histopathology, J. Mt. Sinai Hosp. **5**:432, 1938.

13. Jacoby, G. W.: Subacute Progressive Polymyositis, J. Nerv. & Ment. Dis. **15**:697, 1888.

scopic examination of the kidneys post mortem shows that the major changes are nearly always dependent on vascular disease in the capillary loops in the glomeruli ("wire-loop lesions," "hyaline thrombi"), sometimes on that in the larger vessels on both the arterial and the venous side; in some instances, also, there is additional involvement in the nature of "glomerulonephritis" of restricted or more widespread distribution. The clinicopathologic significance of these lesions will be discussed later in connection with the vascular concept of this disease.

Early in the clinical course examination of urinary specimens may reveal no abnormalities, from which it may be supposed that the renal tissue is spared. This I have observed on a score of occasions, yet it is difficult to be certain in all instances that these organs were really free from disease. On the other hand, I have encountered a number of cases in which the cutaneous phase antedated the systemic phase by as long as from one to two years or more. Postmortem correlation indicates that in other cases, at least, the kidneys may be affected in a subclinical fashion, so to speak. At necropsy it is common to observe gross evidence of closure of small vessels in many instances, if a careful examination is made. There are, however, other cases in which the gross appearance of these organs seems to be normal; yet minute anatomic studies reveal important vascular alterations. In the days before this was sufficiently appreciated, the kidneys were often discarded, with the result that these vascular changes were overlooked or were observed so infrequently as to occasion little curiosity regarding their possible significance. In most instances the observer may expect to find these alterations when examinations of urinary specimens show formed elements, including red blood cells, but it must be stressed that the vascular changes may be minimal and sometimes absent. Often the glomeruli are affected in what seems to be a patchy distribution. Azotemia is usually of moderate grade because, as it has been stated, the lesions are irregularly distributed and because these patients often succumb prematurely to a complicating disease such as bronchopneumonia. There are, however, occasional instances showing marked nitrogen retention approximating that associated with uremia, and the clinical picture of the latter may occasionally be simulated.[14] In such examples, also, the specific gravity of the urine may be fixed at 1.010. The superimposition of terminal bacteremia, with the formation of abscesses in the kidneys, is one of the most likely causes in the production of a grade of azotemia comparable to that occurring in uremia.

14. Keil, H.: The So-Called Libman-Sacks Syndrome, Arch. Dermat. & Syph. **34**:124 (Jan.) 1936; in discussion on Osler, W.: On the Visceral Manifestations of the Erythema Group of Skin Diseases (cases 19 and 26), Am. J. M. Sc. **127**:1, 1904; footnote *2 b*.

On the other hand, there are numerous cases in which the features of nephrosis or of the nephrotic phase of glomerulonephritis may be simulated, owing to the following causes: 1. A tendency to, or actual, inversion of the albumin-globulin ratio. The total protein may be somewhat diminished, or, if the content of globulin is increased, as sometimes occurs, the total content of protein may be within normal limits. 2. A slight increase in the amount of cholesterol in the blood. Extreme hypercholesteremia, such as that often encountered in instances of nephrosis or the nephrotic phase of glomerulonephritis, I have but rarely observed in cases of systemic lupus erythematosus. In other instances the cholesterol value is normal or even diminished, and this is sometimes observed even in association with a diminished total value for protein and with a tendency to inversion of the albumin-globulin ratio. 3. The occurrence of edematous collections of fluid in various parts of the body, especially the serous cavities. 4. A moderate or slight increase in blood pressure. In occasional instances extreme hypertension may be found. The variations in the blood pressure will be discussed conveniently at the end of this section for purposes of contrasting this phenomenon with that occurring in cases of dermatomyositis. In any event, there is usually no particular difficulty in distinguishing the nature of the renal changes in systemic lupus erythematosus from that of the alterations in other types of degenerative, inflammatory or vascular diseases in the kidneys, provided the entire clinical picture is taken into consideration and judged on the basis of previous postmortem observations.

In some instances of systemic lupus erythematosus the globulin value in the blood seems to be somewhat elevated, but according to the cases under my observation this characteristic is not constant. The point will be referred to again in the section concerned with serology.

In a consideration of dermatomyositis the data are more difficult to evaluate for at least two reasons: (1) the inclusion of cases showing "transitional" features, and (2) the pitfalls created by drawing conclusions on the sole basis of the findings in urinary examinations. Oppenheim [15] stated that nephritis is a common complication in cases of dermatomyositis, but he did not offer adequate evidence to substantiate this thesis, nor did he define what he meant by nephritis, though it is to be presumed that he was speaking of the inflammatory type. In Korniloff's case,[16] the status of which is debatable, the patient had glomerulonephritis, but whether this was coincidental remains controversial. In most of the few cases cited as showing evidence of

15. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, ed. 7, Berlin, S. Karger, 1923. vol. 1, p. 840.

16. Korniloff, A. A.: Polymyositis primaria acuta, Deutsche Ztschr. f. Nervenh. 9:119, 1896.

nephritis, the urinary specimens contained a variable amount of albumin, with occasional casts;[17] sometimes such findings seemed to be correlated with a febrile state, but in other instances this explanation appeared not to be applicable. In Fahr's case,[17e] for example, an examination of urine performed late in the course showed albumin, casts and white blood cells; yet the kidneys post mortem were apparently free from significant alterations. In the protocols recorded by Steinitz and Steinfeld[18] and by Schill[19] mention was made of the appearance of a few red blood cells in the urine; in these instances the findings seemed to be correlated best with the factor of cardiac failure accompanied by chronic passive congestion in the kidneys.

There are a few recorded instances of dermatomyositis in which gross hematuria was encountered. This was also noted in cases 2 and 5 described in my previous report.[1] In case 2 the hematuria seemed to be part of a generalized bleeding tendency that manifested itself at the time; a similar occurrence was also noted by Schuermann.[3b] In Batten's[20] patient painless hematuria appeared, but at postmortem examination this was discovered to be caused by a stone in the ureter. Köster[21] recorded the occurrence of hematuria in 1 instance, but this case was probably an unusual example of the Henoch-Osler-Schönlein group, and, indeed, Köster was not certain of the precise classification of that case. Critical analysis of recorded data, therefore, shows how difficult it is to draw absolute conclusions in the absence of a carefully performed postmortem examination. Except in rare instances,[17d] there is usually no impairment in the concentrating power of the urine. In the unusual example described by Talbott and his co-workers,[22] the urinary specimens collected early in the course showed no abnormalities

17. (*a*) Syndenstricker, V. P., and Thomas, D. R., Jr.: Dermatomyositis, Ann. Int. Med. **8**:959, 1935. (*b*) Senator, H.: Ueber acute und subacute multiple Neuritis und Myositis, Ztschr. f. klin. Med. **15**:61, 1889. (*c*) Strümpell, A.: Zur Kenntnis der primären acuten Polymyositis, Deutsche Ztschr. f. Nervenh. **1**:479, 1891. (*d*) McLester, J. S.: Dermatomyositis, Tr. A. Am. Physicians **41**: 283, 1926. (*e*) Fahr, T.: Zur Frage der Polymyositis (Dermatomyositis), Arch. f. Dermat. u. Syph. **130**:1, 1921. (*f*) Hepp.[11]

18. Steinitz, H., and Steinfeld, F.: Untersuchungen zum Creatin-Stoffwechsel bei Dermatomyositis, Ztschr. f. d. ges. exper. Med. **79**:319, 1931.

19. Schill, E.: Ueber einen Fall von Polymyositis, Wien. Arch. f. inn. Med. **12**:353, 1926.

20. Batten, F. E.: Case of Dermatomyositis in a Child, with Pathological Report, Brit. J. Child. Dis. **9**:247, 1912.

21. Köster, H.: Zur Kenntnis der Dermatomyositis, Deutsche Ztschr. f. Nervenh. **12**:150, 1897-1898.

22. Talbott, J. H.; Gall, E. A.; Consolazio, W. V., and Coombs, F. S.: Dermatomyositis with Scleroderma, Calcinosis and Renal Endarteritis Associated with Focal Cortical Necrosis: Report of a Case in Which the Condition Simulated Addison's Disease, with Comment on Metabolic and Pathologic Studies, Arch. Int. Med. **63**:476 (March) 1939.

in the specific gravity or in formed elements; yet one week before death the specific gravity became fixed at 1.010 and the postmortem examination seemed to explain this feature satisfactorily, for there was observed a remarkably widespread subintimal proliferative lesion in the interlobular arteries in the kidneys, with secondary effects on the renal parenchyma. Even in this case blood was apparently not present in the urine.[23]

The few cases in which there was the most definite clinical evidence of renal damage appeared to be the ones in which the condition resembled systemic lupus erythematosus closely; for example, the instance recorded by Weber and Gray.[24] As the patient in this case recovered, the point could not be definitely substantiated by minute anatomic studies. In any event, such cases are uncommon. In Lane's [25] case the urinary specimens showed no abnormalities, yet there was a definite tendency to reversal in the albumin-globulin ratio, chiefly due to an increase in the globulin fraction, with a cholesterol value that was, perhaps, slightly increased. It is probable that in some instances the albumin fraction may be diminished owing to widespread loss of protein in the edematous fluid that is poured out into the muscular and subcutaneous tissues in dermatomyositis. It is doubtful whether the kidneys of Lane's patient were damaged; it is possible, however, as is the case in systemic lupus erythematosus, that urinary findings may be normal for varying periods. A follow-up study of such cases is therefore an essential part of the study.

Both diseases may be attended occasionally by a moderate degree of hypertension. In rare cases the rise in blood pressure may be marked. According to my observations, this phenomenon is more likely to be encountered in cases of systemic lupus erythematosus, owing chiefly to widespread involvement of the glomerular capillaries, and, perhaps, to superimposed infarction or simultaneous glomerulonephritis. It cannot, however, be said that the anatomic changes can be precisely correlated with the degree of hypertension, and it seems probable that extraneous factors sometimes enter, for example, the superimposition of abscesses in the kidneys owing to complicating bacteremia. I have encountered several instances of systemic lupus erythematosus in which the clinical

23. The status of the case recorded in footnote 22 is not entirely clear. The vascular lesions described by these authors are similar to those recorded in a few examples of scleroderma. This case is interpreted best, in my view, as one of scleroderma with secondary and concomitant muscular changes. Yet, because it is difficult to be certain, it may be more reasonable to regard the condition as sub judice.

24. Weber, F. P., and Gray, A. M. H.: Chronic Relapsing Polydermatomyositis with Predominant Involvement of the Subcutaneous Fat (Panniculitis), Brit. J. Dermat. **36**:544, 1924.

25. Lane, C. W.: Dermatomyositis, South. M. J. **31**:287, 1938.

features simulated the nephrotic phase of glomerulonephritis, with moderate elevation of the blood pressure;[26] indeed, in 1 case under my observation the nature of the condition was misunderstood because of failure to evaluate the significance of the eruption that had been present at the time of the patient's previous admissions. When the cutaneous lesions fade, as they often do in the terminal phases, the diagnosis becomes more difficult, and in such cases the postmortem observations assume great importance. It must be stressed that in the average example of systemic lupus erythematosus an appreciable elevation in the blood pressure generally does not occur; nevertheless, hypertension does occur for various reasons, and I can therefore substantiate the observations of Rose and Pillsbury,[26a] who reported a number of such examples of systemic lupus erythematosus.

In occasional cases of dermatomyositis there is a moderate elevation in the blood pressure. Thus, Fahr[17g] recorded the protocol of 1 such instance and, as the kidneys were apparently free from significant alterations, he was inclined to attribute the hypertension to the occurrence of widespread arterial disease in the muscles. I have encountered 1 example of dermatomyositis in which the blood pressure became more elevated and reached a level of 200 mm. systolic with a correspondingly increased diastolic pressure; here again, the renal findings were apparently insufficient to explain the phenomenon, supporting to a certain extent the conclusion reached by Fahr. Yet it is extremely common to encounter instances in which widespread muscular disease is present, with or without what one might call pronounced vascular changes, and the blood pressure maintains itself at a normal level. Why hypertension occurs in some instances and whether it is related to the type of vascular alteration observed in the arteries in the muscles are questions to which the present knowledge fails to provide satisfactory answers. It is even possible that the 2 cases of hypertension just discussed may have been coincidental in the sense of having a complicating essential hypertension in the early stages. In the case reported by Talbott and his associates,[22] in which there occurred marked changes in the interlobular arteries with partial necrosis of the renal parenchyma, there was no rise in blood pressure; on the contrary, the outstanding feature was a "postural hypotension," which was regarded as evidence supporting the original diagnosis of Addison's disease.[23]

In general, then, the clinicopathologic features are in harmony with the observations on the blood pressure, and the evidence indicates that the kidneys are, as a rule, spared in dermatomyositis.

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26. (*a*) Rose, E., and Pillsbury, D. M.: Acute Disseminated Lupus Erythematosus: A Systemic Disease, Ann. Int. Med. **12**:951, 1939. (*b*) Keil.[5g] (c) Tremaine.[5] (*d*) Friedberg, Gross and Wallach.[7]

7. *Ophthalmoscopic Observations.*—In systemic lupus erythematosus the fundi often reveal alterations. The evidence appears to indicate that these changes arise primarily in relation to the blood vessels and that they represent but one of the manifestations of a systemic disease. Their occurrence cannot be precisely correlated with the severity of the clinical course, nor can any deductions be made regarding the immediate prognosis. In general, however, such changes may be regarded as another evidence that the condition has become systemic. Ophthalmoscopic examination reveals in most instances that the hemorrhages and soft (fluffy) exudates are arranged in general in a perivascular fashion. It is doubtful whether such appearances are pathognomonic of systemic lupus erythematosus. In view of the fact that the blood pressure is usually within the limits of normal and in view of the nature of the data on the other manifestations of the disease (for example, embolism is extremely unlikely, and blood cultures are sterile), it seems reasonable to conclude that the lesions are of local origin. Furthermore, it is likely that the pathologic alterations will be found to be analogous to those seen in other organs; in all probability the exudates noted are simply collections of edematous fluid, with properties similar to those exhibited by the edematous fluid in the upper part of the corium skin. Peripapillary edema of varying severity occurs more commonly than is generally suspected; of this phenomenon I have seen 3 striking examples, and I have notes on several others. In the case of this anomaly too, knowledge of the other features of the disease would lead me to believe that this is dependent on vascular damage, with the "transudation" of edematous fluid in relation to the papilla. There is no evidence that this type of papilledema is caused by an increase in the intracranial pressure or by such pressure as that on the large structures in the eyeball. In nearly all the instances under my observation the patient recovered from the immediate attack, the changes in the eyegrounds subsiding completely. Such periods of spontaneous resolution are merely more or less prolonged remissions in a condition that, according to my observations, eventually suffers a recrudescence with fatal issue. Goldstein and Wexler [27] recorded an unusual case of atrophy of the optic nerves associated with alterations in the retinal arterioles chiefly, and they showed definitely that the areas of punched-out atrophy seen ophthalmoscopically were related probably to the pathologic changes in the vessels in the retina, as contrasted with the chorioretinitis observed in instances of "sepsis." This case, which I had the opportunity of studying many years ago, is unique in the occurrence of bilateral atrophy of the optic nerves, but the relation of this finding remains unclarified in my mind in view of the fact that at the

27. Goldstein, I., and Wexler, D.: Retinal Vascular Disease in a Case of Acute Lupus Erythematosus Disseminatus, Arch. Ophth. **8**:852 (Dec.) 1932.

same time the spinal fluid showed a colloidal gold curve of the paretic type.[28] In any event, Goldstein and Wexler deserve great credit for their thorough pathologic studies, which showed that the major changes were of retinal origin. Abramowicz and Dulewicz[29] recorded the occurrence of oval edematous foci in the fundus of a patient afflicted with acute lupus erythematosus and stated that these resembled "retinitis guttata" as described by Dimmer in association with arteriosclerosis and other diseases of unknown cause; however, no pathologic studies were made. On the other hand, Semon and Wolff[30] described a few round, slightly raised, whitish areas in the disks occurring in a case of fatal systemic lupus erythematosus; these lesions bore only a superficial resemblance to choroidal tubercles. Microscopic examination revealed that the major alterations were in the choroidal layer, with a well marked subretinal inflammatory exudate showing a tendency to repair. In this instance the patient complained of misty vision. Recently, Klauder and Ellis[31] observed a man aged 36 years who was afflicted with systemic lupus erythematosus of relatively short duration; early in the course the patient complained of blurring of vision. Ophthalmoscopic examination revealed various-sized, fluffy, cloudlike patches throughout the fundus, especially around the disks, with a few small hemorrhages around the macula. The visual acuity was 3/60 in each eye. In the discussion of this case, Lillie stated that he regarded the changes as those of diffuse perivasculitis and periphlebitis.

Despite fairly extensive changes in the fundi, it is uncommon to encounter patients who complain of subjective symptoms of visual disturbances, such as haziness of vision. In addition to the case described by Goldstein and Wexler, I have observed 1 other example in which there was blindness, attributed to an "embolism" of the central retinal artery with secondary glaucomatous change in the affected eye. As this followed an intravenous injection of a gold compound, it seems difficult to be certain of the precise genesis, though it seems possible that this might have been due to a local vascular closure.

Finally, Pillat[32] observed choroidal foci in the peripheral portions of the fundus at sites of slowing of the circulation; these changes were probably old, as indicated by the presence of a peripheral ring of pig-

28. Records of the Mount Sinai Hospital, New York City, Postmortem 7762, May 7, 1931 (A. K.).

29. Abramowicz, I., and Dulewicz, M.: Le fond de l'oeil dans le lupus erythematodes acutus (erythema perstans), Ann. d'ocul. **170**:599, 1933.

30. Semon, H. C., and Wolff, E.: Acute Lupus Erythematosus with Fundus Lesions, Proc. Roy. Soc. Med. **27**:153, 1933.

31. Klauder, J. V., and Ellis, V. M.: Effective Treatment of Lupus Erythematosus and Exudative Retinitis with a Gold Compound, Arch. Ophth. **21**:893 (May) 1939.

32. Pillat, A.: Ueber das Vorkommen von Chorioiditis bei Lupus erythematodes, Arch. f. Ophth. **133**:566, 1935.

mentation. In most of the cases these patches were unilateral, and in 2 instances there were fresh alterations. These areas of choroiditis were encountered in one third of 48 examples of lupus erythematosus, and on the basis of their attributes, though atypical in some respects, Pillat said that he was inclined to attribute them to tuberculosis. In 4 instances also, there were old changes in the cornea (keratitis eczematosa), residues of an old process which probably had its onset in youth. Pillat stressed the asymptomatic nature of these findings. It is evident, from a perusal of his report that there was no precise relation between these lesions as described and the nature of the lupus erythematosus, except, perhaps, in 2 of the cases, and even in these instances there is room for considerable doubt. Furthermore, the nature of these choroidal changes becomes even more debatable when it is found that Pillat [33] observed similar lesions in 60.7 per cent of 28 cases of acute polyarthritis. If one assumes that these changes were of tuberculous nature, which seems likely, it becomes clear that this is additional evidence for believing that the population of Vienna is, or was, heavily infected with tuberculosis (morbus viennsis).

The alterations previously mentioned as occurring in systemic lupus erythematosus have not yet been submitted to thorough microscopic examination. These changes, as has been indicated, are capable of complete restitution to normal, at least temporarily, and it is likely that any pigmentary disturbances in such areas would be dependent on the extravasation of blood pigment (positive iron stain). Such lesions, furthermore, seem not to acquire a peripheral ring of pigmentation.

In cases of dermatomyositis ophthalmoscopic examinations generally reveal no abnormalities, though there are exceptions to this rule. In comparison with those associated with systemic lupus erythematosus changes in the fundi are comparatively uncommon. In this respect dermatomyositis seems to behave more like a localized disease than does systemic lupus erythematosus. In 1933 Grönblad [34] made an interesting contribution in a paper describing the ocular lesions in 3 cases of poikilodermatomyositis, a condition that appears to be identical with ordinary dermatomyositis. Grönblad recorded the following observations: the occurrence of edema localized to the peripapillary region, these changes being apparently situated deeply, without definite relation to the retinal vessels; peripheral isolated round spots which seemed to lie in the neighborhood of fine retinal vessels and which he interpreted as atrophic; edema of the vitreous at the macula, similar to the peripapillary edema, and in 1 case the appearance of a small hemorrhage that disappeared in two weeks. Visual acuity was normal. Grönblad noticed

33. Pillat, A.: Ueber Augenhintergrundsbefunde bei akuter Polyarthritis, Wien. klin. Wchnschr. **48**:303, 1935.

34. Grönblad, E.: Des alterations oculaires dans la poikilodermatomyositis, Acta ophth. **11**:461, 1933.

that in 2 of the 3 cases it was difficult to dilate the eyes, a circumstance which he thought was attributable to muscular disease. Ocular disease involving the small muscles of the eyes is encountered occasionally in cases of dermatomyositis; it is probably extremely rare in those of ordinary systemic lupus erythematosus. Recently, Bruce [35] recorded the occurrence of "retinitis" associated with 3 interesting examples of dermatomyositis, 2 of these concerning children. Of the patients in this group 2 recovered, despite extensive changes in the fundi. In all the patients the retinal veins were somewhat distended, occasionally indented by arteries that were normal in appearance. Scattered throughout the fundi were varying numbers of grayish yellow exudates that seemed, for the most part, to be superficially located and resembled the "cotton-wool" exudates of albuminuric retinitis; some of the smaller areas were apparently deeper in situation and simulated choroidal tubercles (case 2). Some of the exudates were in relation to the maculas (cases 1 and 2), while in 2 instances there was slight haziness of the disk margins (cases 2 and 3). In all 3 instances there were superficial or deeper hemorrhages, generally lying along the course of veins. The second patient in the group complained of dimness of vision, but the severity of the illness or the age of the subjects prevented Bruce from obtaining data on the visual acuity and fields. The patient in case 1, a girl of 11 years, died; microscopic examination of the posterior poles of the eyes revealed edematous and hemorrhagic changes in the retinal layers, but postmortem changes obscured many of the finer details. In any event, the alterations described were in harmony with the clinical findings. The observations recorded by Bruce seem to be similar to those just described in the section on systemic lupus erythematosus. In this connection it is pertinent to say that I once observed an instance of hemorrhages and exudates in the fundus of a patient who complained of severe pains in the muscles and subcutaneous tissues; the course was rapidly fatal, and postmortem examination revealed possible lymphatic leukemia of an atypical type.

It will be seen, then, that the changes in the fundus oculi, probably of a nonspecific nature in a clinical sense, are observed with regularity in cases of systemic lupus erythematosus and less commonly in those of dermatomyositis and its clinical congeners.

8. *Cardiac Involvement.*—(*a*) Endocardial Disease: In a considerable percentage of cases of systemic lupus erythematosus, roughly in from 30 to 50 per cent, there occurs gross evidence of pathologic changes in the endocardium, both valvular and mural. Credit is due Libman and Sacks [36] who in 1923-1924 first clearly recognized atypical

35. Bruce, G. M.: Retinitis in Dermatomyositis, Tr. Am. Ophth. Soc. **36**: 282, 1938.

36. Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch. Int. Med. **33**:701 (June) 1924.

verrucous endocarditis, which they found in 4 cases. The patients in these cases showed clinical features simulating both rheumatic fever and subacute bacterial endocarditis, yet differing in many respects from these two conditions. In 2 of their cases there were observed eruptions that the consulting dermatologist was unwilling to identify as lupus erythematosus, but current knowledge indicates that undue stress was laid on obsolete criteria. In 1930 I recognized that systemic lupus erythematosus may occur without gross endocardial changes post mortem.[36a] Earlier in that year there came under my observation an instance of systemic lupus erythematosus in which the occurrence of atypical verrucous endocarditis was diagnosed correctly; yet at post-mortem examination the endocardial changes appeared too slight to have occasioned conspicuous clinical signs of valvular disease. In 1932 Gross [37] recorded an outstanding study of the pathologic anatomy of atypical verrucous endocarditis, with particular reference to the valvular alterations and the vascular changes in the myocardium. Of special importance was his description of the "pocket lesions" in this condition. The microscopic features in this type of endocardial disease as observed in the valves, the chordae tendineae and the mural portion of the endocardium, the tendency to involve the right side of the heart, often to the exclusion of the left side and other characteristics of the condition, were described by Gross in great detail.[38]

There is ample evidence that this variety of cardiac disease is not related directly to that seen in cases of rheumatic fever,[38a] although the

36a. In a paper by Baehr (Baehr, G.: Renal Complications of Endocarditis, Tr. A. Am. Physicians **46**:87, 1931) mention was made of 2 cases of systemic lupus erythematosus without gross valvular changes. These examples, which were not included in the statistics, were given to Baehr by me in a list of cases that I had gathered in 1930 from the records of the Mount Sinai Hospital. These cases as well as many others on the list had been buried in the records under a wide variety of diagnoses. Also, the section of skin demonstrated at the meeting of the association had been sectioned and stained by me.

37. Gross, L.: The Heart in Atypical Verrucous Endocarditis (Libman-Sacks), in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, p. 527.

38. Gross, L.: The Cardiac Lesion in Libman-Sacks Disease with a Consideration of Its Relationship to Acute Disseminated Lupus Erythematosus, to be published; manuscript and revisions in possession of Dr. E. Libman, New York.

38a. A few cases of systemic lupus erythematosus are complicated by acute bacterial endocarditis, rarely by subacute bacterial endocarditis. These complications occur probably late in the course of the disease and in all likelihood are not an esssential part of it. I have seen an instance of discoid atrophic lupus erythematosus in a patient with rheumatic heart disease, confirmed at necropsy; the two conditions were probably coincidental and unrelated. Every case of endocardial lesions must therefore be evaluated critically on the basis of a knowledge of the various types of endocardial changes seen in association with this disease.

occasional association of chronic valvular alterations still requires clarification. There are, moreover, occasional instances in which the body of the valves, generally the mitral or the tricuspid valve, shows evidence of an inflammatory process that, according to Gross, may be differentiated from rheumatic valvulitis by the local pathologic features and the general sparing of the ring; when, as may happen occasionally, the ring is invaded by systemic lupus erythematosus, the changes are still distinguishable from the characteristic lesion in rheumatic heart disease. These statements are based on the microscopic criteria elaborated by Gross.[38]

Notwithstanding the nosologic importance of atypical verrucous endocarditis, it seems probable that the area of distribution of these verrucae and the manner in which they are deposited contribute but little to the signs and symptoms in this disease. Most of the audible murmurs are, in all likelihood, attributable to extraneous factors, except in the relatively uncommon cases in which old valvular changes are encountered. The simultaneous occurrence of a pericardial rub makes the existence of gross endocardial involvement more probable, as these two parts of the cardiac structure are often concurrently affected, but this rule has exceptions.[14] In a succeeding paragraph an attempt will be made to evaluate the significance of nonbacterial thrombotic endocarditis as described by Friedberg, Gross and Wallach,[7] for this subject seems destined to have some relation to systemic lupus erythematosus.

In typical instances of dermatomyositis the endocardium seems to be spared, except possibly in occasional cases. Thus, Potain [39] described a slight marginal thickening in the mitral valve, apparently of recent origin, as it was red and showed deposition of small granulations on the surface (fibrinous, nonadherent). The nature of the endocardial changes, whether truly significant or not, must remain a debatable question here. Jollasse [40] recorded an unusual instance of polymyositis (no rash present) in which the postmortem examination revealed a verruca on one aortic leaflet, with obliteration of the pericardial cavity; it seems fair to note that the precise classification of the type of polymyositis in this case has been questioned, with considerable justification, by other critical observers, and the status of the entire case is best considered sub judice. It must be admitted, however, that extensive studies on this phase of the subject, such as were made by Libman and Sacks [36] and by Gross,[41] are still lacking, and it seems wise to suspend judg-

39. Potain: Morve chronique de forme anomale, Bull. et mém. Soc. méd. d. hôp. de Paris **12**:314, 1876.

40. Jollasse, O.: Ueber acute primäre Polymyositis, Mitt. a. d. Hamb. Staatskrankenanst. **1**:326, 1897.

41. Gross (footnotes 37 and 38).

ment. There is reason to believe that in rare instances rheumatic heart disease may be encountered coincidentally. Marcus and Weinstein [42] cited a number of references pertaining to cases in which the conditions were diagnosed as rheumatic fever, but a critical analysis of these as well as of a few other examples in the literature indicates clearly that the clinicopathologic criteria for the diagnosis of rheumatic heart disease were not fulfilled. In 2 of the cases cited in my previous report the conditions were also diagnosed as rheumatic heart disease, but the postmortem examinations did not substantiate this diagnosis.[1]

(*b*) Myocardial Involvement: In systemic lupus erythematosus the myocardium is generally spared, at least in a clinical sense. Tachycardia is frequent, but it is usually not so striking as in dermatomyositis. Cardiac failure is relatively uncommon and predominantly right sided, and generally finds its explanation in widespread vascular changes such as those in the pulmonary arterioles. Evidence of myocardial damage is often first encountered in connection with the study of electrocardiograms, especially those taken serially, but the changes are probably nonspecific. The most common alteration is low voltage in all leads, interpreted as indicating damaged cardiac muscle; changes in the other waves and, especially, occasional prolongation of the PR complex may also be observed. Postmortem examination often shows involvement of the arterioles and scattered small areas of infarction that probably correspond to the points of vascular closure.[37] It is important to stress the consistent absence of Aschoff bodies in the heart. In observations made many years ago, I noted marked dilatation of the capillaries, which teemed with blood cells; it is possible that this represents a terminal phenomenon in these cases, and it may be encountered in other organs as well.

In dermatomyositis symptoms and signs referable to the myocardium are more frequent than has been commonly believed. Persistent tachycardia, often observed even in the afebrile periods, may be an outstanding feature; its occurrence during convalescence may be regarded as an evidence of activity in the process, despite involution in the other manifestations. In other cases the patients may have palpitations, dyspnea, edema, cyanosis and pallor and perhaps arrhythmia, but it is not clear in all instances that the complaints are truly of cardiac origin; each case has to be individualized. A few observers have recorded electrocardiographic evidence of myocardial damage,[43] but the studies on

42. Marcus, I. H., and Weinstein, J.: Dermatomyositis: Report of a Case with a Review of the Literature, Ann. Int. Med. **9**:406, 1935.

43. Friedman, E. D.: Dermatomyositis, M. J. & Rec. **123**:382, 1926. Marcus and Weinstein.[42]

this phase of the subject are still fragmentary.[43a] In some instances there is a definite degree of congestive heart failure associated with the usual signs of this complication. An occasional investigator has found slight evidence of myocardial degeneration, such as swelling and early pyknosis of the nuclei in individual fibers,[44] a mild degree of fatty degeneration [18] as well as scattered areas of edema with notable dilatation of the capillaries and occasional formation of a fibrinous thrombus within these vessels. These and similar changes seem not to be pathognomonic, or even highly characteristic, of dermatomyositis, and most observers have felt that these alterations are disproportionately mild when compared to the severe process in the voluntary striated muscles. However, Lorenz [45] reported the occurrence of hemorrhagic areas in the myocardium of 4 patients who were afflicted with hemorrhagic polymyositis and noted a reciprocal relation between the extent and severity of the alterations in the voluntary striated muscles and those of the changes in the cardiac musculature. The relation of these conditions to ordinary dermatomyositis is, however, still unsettled, but Lorenz was aware of the fact that occasionally relatively severe changes may be observed in the myocardium of patients with ordinary dermatomyositis. In the cases recorded by him the supervention of this complication caused sudden death or a rapidly fatal course. On the whole, then, the ordinary typical examples of dermatomyositis show no pathognomonic lesions in the heart, and only occasionally are the symptoms referable to this organ sufficiently pronounced to obscure the characteristic manifestations of this disease.

(*c*) Pericardial Disease: In systemic lupus erythematosus involvement of the pericardium may be accompanied by an audible rub; such murmurs or indistinguishable ones may also be produced sometimes by pleuropericardial disease. Involvement of the pericardium is generally associated with atypical verrucous endocarditis or variants of it, but this rule can be applied only in a broad manner. Fairly large effusions may occur in this cavity and reveal themselves by roentgenographic and clinical examinations. Finally, the changes found in the pericardium may be more chronic, presenting but one of the sites of chronic polyserositis. Postmortem examination reveals often small

43a. There is reason to believe that in some instances of dermatomyositis the electrocardiograms show low voltage due to increased resistance to the electric current imposed by widespread edematous infiltrations involving the muscles, subcutaneous tissues and even the cutis. Consequently, such findings in the electrocardiograms do not always constitute positive proof of myocardial damage.

44. Ingram, J. T., and Stewart, M. J.: Dermatomyostis and Poikilodermia, Brit. J. Dermat. **46**:53, 1934

45. Lorenz, H.: Herzerscheinungen bei der akuten Polymyositis und deren Beziehungen für die Diagnostik der Letzteren, Deutsche med. Wchnschr. **32**: 777, 1906.

patches of pericarditis, fresh or old, sometimes more extensive lesions and occasionally more or less firm adhesions between the leaflets of the cavity with a corresponding degree of obliteration. The subject will be further discussed under the caption of serous membranes.

In dermatomyositis the pericardium may contain fluid of varying amounts, but this is generally uncommon and probably the result of an element of cardiac failure. It is therefore seen far less often in dermatomyositis than in systemic lupus erythematosus, and generally owes its origin to a different cause. In other words, involvement of the serous surfaces, common in systemic lupus erythematosus, is apparently not a feature in ordinary dermatomyositis. The only exception with which I am acquainted is the case of Jollasse,[40] in which there was adhesive pericarditis, but, as stated before, the nature of the polymyositis in this example appears to be debatable.

(*d*) Cardiac Failure: As a rule, systemic lupus erythematosus is not terminated by myocardial failure, for the patient dies long before such changes become manifest. In occasional examples right-sided cardiac failure may be encountered in the course of this disease, and it is usual to observe then that the vascular pathologic alterations have shown a special predilection for the pulmonary circulation. It is, however, possible that there may be occasional exceptions to this rule.

Failure of the right side of the heart in varying degrees may be encountered proportionately more often in cases of dermatomyositis, and it is to be correlated with degenerative myocardial damage as well as with the strain placed on the heart by other complications, such as the respiratory symptoms. Involvement of the pulmonary vessels, in a manner analogous to that in cases of systemic lupus erythematosus, seems to be excessively rare. In instances of hemorrhagic polymyositis, which may possibly be regarded as a congener of ordinary dermatomyositis, cardiac failure is generally due to involvement of the right ventricle, but occasionally the left side of the heart is also affected by extensive hemorrhage; sudden death is therefore occasionally encountered.

9. *Disease in the Serous Membranes.*—Involvement of the serous membranes represents a feature of great importance in systemic lupus erythematosus. Though cardiac and renal factors may sometimes contribute to render these manifestations more prominent, disease in the serous membranes is generally primary and independent. Symptoms referable to this condition are often encountered early in the course (for example, pleural friction rub), intercurrently (for example, enlargement of the heart due to pericardial effusion) and, finally, as one of the outstanding features in the disease (polyserosal form of systemic lupus erythematosus; for example, accumulations of ascitic fluid and occasional attacks of abdominal pain). Involvement of these cavities and their coverings is generally recognizable during life; involvement

to milder degrees which gives rise to few or no symptoms may be observed post mortem (localized patches of serofibrinous or fibrous pericarditis as well as localized similar implication of the pleurae, which is common, and of the peritoneum, which is relatively uncommon).

In dermatomyositis phenomena referable to these membranes are but rarely encountered. For example, onset with pleurisy or pericarditis or with the picture of chronic polyserositis is almost unknown. Abdominal pain is generally found, on close examination, to be caused by involvement of the abdominal musculature (case 5 previously reported [1]). I am excluding a few instances of dermatomyositis in which accumulations of fluid were observed in the various cavities; in these cases the clinical picture of serous involvement was not striking, and the manifestations, which were generally first discovered at necropsy, appeared to be either dependent on a degree of cardiac failure, usually of a progressive, insidious type, or secondary to some other cause, such as a pneumonic process accompanied by pleural adhesions.

In this respect, then, the clinical pictures of systemic lupus erythematosus and dermatomyositis seem to show important differences.

10. *Anomalies of the Lymph Nodes.*—Systemic lupus erythematosus is often accompanied by moderate enlargement of the lymph nodes, localized (cervical, axillary) or generalized.[46] There are, however, instances in which the cervical glands become as large as a fist or even larger, persist in this form for varying periods or break down with the extrusion of necrotic, often infected, tissue. It appears that this is what used to be called "scrofulous" glands (a few cases were undoubtedly tuberculous, which is to be expected in populations heavily infected with the disease); under this term, however, many instances of nontuberculous infections of lymph nodes were often included.[2a] The superficial lymph glands show, on microscopic examination, a nonspecific hyperplastic condition and in occasional instances areas of necrosis of nontuberculous nature. In the case reported by Ginzler and Fox [47] the prominence of the latter feature first suggested the diagnosis of tularemia.

In addition to the superficial lymph nodes, the deeper ones are also involved. Postmortem examination reveals frequently a generalized enlargement of the lymph nodes in the chest and in the abdomen; in the latter situation they may constitute a striking feature. Those in the chest (tracheobronchial chain) are sometimes complicated by tuberculous caseation in varying stages of healing, generally restricted in extent, occasionally more widespread within individual lymph nodes. It seems

46. Keil, H.: (*a*) Tuberculous Skin Lesions, New England J. Med. **218**: 783, 1938; (*b*) footnote *2b*.

47. Ginzler, A., and Fox, T. T.: Disseminated Lupus Erythematosus in a Youth, with Some Unusual Findings, Arch. Path. **26**:916 (Oct.) 1938.

probable that the few instances of miliary tuberculosis complicating systemic lupus erythematosus may have been caused by a lighting up of such foci, a phenomenon that probably also occurs intercurrently in the course of other diseases. The lymph nodes in the abdomen are generally succulent in appearance and moderately enlarged; on cross section they show an edematous aspect, occasionally scattered areas of necrosis of a yellowish or grayish white color and sometimes discrete foci of hemorrhage. Microscopic examination shows that these necrotic areas are generally free from the ordinary alterations seen in cases of tuberculosis, and tubercle bacilli are not revealed by the Ziehl-Neelsen stain. In previous publications [48] it was stated that the gross appearance of tuberculosis may be simulated in various lymph nodes, especially those in the abdominal cavity; yet, minute anatomic studies failed to reveal changes consistent with those of a tuberculous nature. Exceptions to this rule are relatively uncommon, and all such lymph nodes should be examined microscopically, instead of reliance being placed solely on macroscopic appearances.

In one instance, on which I have notes, the changes in the lymph nodes were regarded by the pathologist as supporting a diagnosis of reticulosis, the case having been presented as a clinical example of Still's disease or Felty's syndrome.[49] In investigating this case, the protocol of which I studied in 1930 together with some of the available material, it became apparent to me that the rash of acute lupus erythematosus and the urinary findings had not been evaluated properly, and, indeed, the kidneys were discarded. This occurred in the days before the clinicopathologic features of systemic lupus erythematosus (such as rash, renal changes clinically and at autopsy, articular manifestations and vascular lesions) were understood and before it was generally appreciated that atypical verrucous endocarditis might be absent grossly in such instances.[36a] The occurrence of "reticulosis," a pathologic change probably nonspecific, was given undue emphasis, and it will be pointed out later that the same has been done in the rare examples of dermatomyositis in which a similar manifestation may be encountered. Here again, it is apparent that the pathologist must be prepared to correlate his observations with the clinical findings in order to avoid overstressing a nonspecific, though not common, alteration.

In cases of dermatomyositis involvement of the lymph nodes, although not infrequently observed clinically, appears to be less common than in those of systemic lupus erythematosus and rarely becomes as pronounced as in cases of the latter disease. It is probable that occasional exceptions

48. Keil (footnotes 2 and 46*a*).

49. Baehr, G., and Klemperer, P.: Clinico-Pathologic Conference at the Mount Sinai Hospital, 1927-1928, case 295924, postmortem 6429. This case involves a typical instance of acute lupus erythematosis with clinical evidence of renal disease, presented by Baehr and Klemperer in the conference as an example of Still's disease or Felty's syndrome in an adult; the kidneys in this case were discarded.

will be found. In several instances I have observed generalized lymphadenopathy, moderate in degree. In Fiedler's patient [50] this was accompanied by some pain. In 1 instance showing features "intermediate" between systemic lupus erythematosus and dermatomyositis,[38] the lymph nodes, among other organs, revealed areas of nontuberculous necrosis, and similar manifestations have been recorded occasionally in the literature. There are, also, a few instances, among them the case recorded by Davison,[51] in which there was an associated nonspecific hyperplastic condition of the more deeply situated lymph glands, a pathologic phenomenon of apparently banal significance.

On the whole, then, lymphadenopathy is a feature encountered more often in cases of systemic lupus erythematosus, in which it sometimes takes on a magnitude and gross appearance simulating tuberculous lymph nodes.

11. *Involvement of the Spleen.*—Splenomegaly may be met with both in instances of systemic lupus erythematosus and in those of dermatomyositis, but in neither disease is it likely to attain an extreme grade. The clinical attributes are not distinctive, and the point is best remembered in a negative way, for there is the possibility of confusion with other diseases. At the postmortem examination the splenomegaly, when present, is likely to show features that differentiate these two conditions from one another.

In cases of systemic lupus erythematosus examination of the spleen may show evidence of vascular closure apparently of local origin (old and fresh infarcts, single or multiple and generally small) or of scattered areas of necrosis; these findings are rare in authentic examples of dermatomyositis. Microscopically, a variety of vascular alterations may be encountered, a description of which is not essential to this presentation. It may, however, be noted that in all probability these changes are not pathognomonic of this disease.

In cases of dermatomyositis enlargement of the spleen is usually attributed to a generalized infection. The spleen is generally firmer than it is in the ordinary acute infections, and on microscopic examination there is observed a hyperplastic pulp, with increase in its constituents and some congestion. Other investigators are of the belief that splenomegaly associated with dermatomyositis is to be regarded as spodogenous, attributable to the absorption of degenerated products in the broken-down muscles.

Here again, systemic lupus erythematosus manifests evidence of its generalization, while dermatomyositis seems to behave more like a

50. Fiedler, E.: Ueber einen Fall von chronischer Polymyositis mit hochgradiger Eosinophilie und periodisch wiederkehrenden fieberhaften Exazerbationen, München. med. Wchnschr. **78**:1176, 1931.

51. Davison, C.: Dermatomyositis: A Clinicopathologic Study; Report of a Case with Complete Necropsy, Arch. Dermat. & Syph. **19**:255 (Feb.) 1929.

restricted infection, with secondary effects on the spleen. A more intensive investigation of this phase of the subject would be desirable.

12. *Disease in the Liver.*—Areas of necrosis, apparently similar to those occurring in the lymph nodes and in the spleen, may be seen occasionally in the liver in cases of systemic lupus erythematosus. Thus far, such an appearance has not been described in connection with authentic cases of dermatomyositis.

13. *Involvement of the Brain.*—The cerebral manifestations of systemic lupus erythematosus have been but little studied. In some instances convulsions form an interesting feature in the clinical picture, and these may be encountered in the absence of a pronounced degree of azotemia. In 1 instance under my observation the spinal fluid of a patient who presented no evidence of syphilis showed a colloidal gold curve of the paretic type; this finding, though rare, seems to have some interest in view of the common observation of a positive Wassermann reaction in cases of systemic lupus erythematosus. Tremaine [5] recorded the occurrence of adhesive meningitis in a single case, and I have observed an instance in which the postmortem examination revealed chronic meningoencephalitis. It is probable that microscopic studies, thus far few, will show vascular alterations in the capillaries and in the somewhat larger vessels. The entire subject is in want of investigation.

In typical instances of dermatomyositis the occurrence of such phenomena has not been recorded.

B. LABORATORY DATA

1. *Urinalyses.*—The subject of the contents of the urine has been discussed in the section devoted to renal disease. The question of porphyrinuria requires fresh and extensive investigations before the data recorded in the literature may be accurately assessed, and it will not be considered here.

2. *Blood Counts.*—In association with both diseases secondary anemia of variable degree may occur. It may be absent in some cases or it may, on the other hand, attain a severe grade within a short period. When the platelet count is reduced, the hematologic formula of aplastic anemia may be simulated, but in these conditions there will be found some evidence of regeneration of the blood elements. The color index is generally below 1.

In cases of systemic lupus erythematosus leukopenia (absolute in many cases, relative in others) is so frequent an occurrence as to justify the rank of an outstanding feature of the disease. It is, however, also encountered in occasional instances of dermatomyositis, though not nearly so often. In instances of both diseases, also, the leukopenia is usually dependent on a decrease in the lymphocytes, and the polymorpho-

nuclear leukocytes generally show a shift to the left in an increase in the young forms. In cases of systemic lupus erythematosus small numbers of abnormal cells of the myelocyte series may be encountered in unusual instances. On the other hand, there are many examples of these diseases, especially systemic lupus erythematosus, in association with which relative lymphocytosis may be observed. In still other cases there may be an increase in the number of monocytes; this is especially encountered in cases of dermatomyositis, but it may also occur in occasional examples of systemic lupus erythematosus. The one apparently distinguishing feature, when it is present, is an increase in the number of eosinophils in instances of dermatomyositis. It used to be thought that muscular disease accompanied by eosinophilia invariably meant trichinosis, but this combination of phenomena may also be seen in association with dermatomyositis. It is believed by many that this feature is dependent on the reaction of the body to the rapid and widespread destruction of muscular tissue. In cases of systemic lupus erythematosus I have not yet encountered a single instance of eosinophilia, either early in the course or as a postinflammatory phenomenon in the few cases in which there is temporary recovery, for example from pneumonia. Exceptions to this rule, if they exist, are probably uncommon, and appear to concern cases illustrating a "transitional state," for instance those with features suggesting systemic lupus erythematosus associated with muscular manifestations of severe grade.

In both diseases leukocytosis occurs commonly in the presence of a complicating infection or suppurative process (such as bronchopneumonia, sinusitis and suppuration of the middle ear). This is of special interest in cases of systemic lupus erythematosus, in which the bone marrow may apparently be depressed, but it is clear that this depression is only relative and may be overcome by other factors, particularly intercurrent infections. In these diseases, but especially in dermatomyositis, this is accomplished by an increase in the polymorphonuclear leukocytes accompanied by relative or absolute lymphopenia. In case 5 of my previous report[1] the white cell count was well over 70,000 with an increase in the polymorphonuclear cells. In dermatomyositis Schuermann[3b] has attributed the lymphopenia to the widespread shunting of lymphocytes into the muscular tissue, the site of the inflammatory reaction, but it seems likely that the bone marrow is simultaneously affected by this disease. In systemic lupus erythematosus the cause of the phenomenon is problematic at present, although one may consider the factor of involvement of the lymph nodes, commonly encountered in association with this condition. A high leukocyte count due to an absolute increase in the eosinophilic cells may be observed in occasional examples of dermatomyositis; under special circumstances the clinical picture would then simulate closely that of periarteritis nodosa.

Diminution in the number of platelets is far more commonly encountered in association with systemic lupus erythematosus, and, indeed, there are instances in which the hematologic formula of thrombopenic purpura may be simulated closely. I have recorded a group of cases in which splenectomy was successfully performed for what was supposed to be ordinary thrombopenic purpura, the apparent cure being succeeded, within eight to ten months or more, by the appearance of systemic lupus erythematosus.[52] It is common to observe in cases of systemic lupus erythematosus marked decreases in the platelet count, with succeeding numeric fluctuations, and it is possible that these may be dependent on the inclusion of thrombocytes within "hyaline thrombi" in the capillaries and somewhat larger vessels; on the other hand, it is not possible at present to eliminate the factor of damage to the bone marrow. Less commonly a similar phenomenon may be encountered in cases of dermatomyositis in which, also, fluctuations in the number of platelets have been observed.[53] In both diseases purpuric lesions may occur in the skin and mucous membranes as a superimposed or independent manifestation.

3. *Metabolic Studies.*—The nitrogen metabolism has been discussed briefly in the section devoted to a consideration of the renal changes. Here it remains to add several other subjects of interest.

(*a*) *Calcium in the Blood.*—In systemic lupus erythematosus the calcium value of the blood is within the limits of normal. There are, however, occasional instances in which this value is diminished independently of renal insufficiency or of a lowered albumin content in the blood and in which there occurs deposition of calcium in the subcutaneous tissues. A few instances may show a definite, though not striking elevation in the blood calcium. The reasons for these variations are at present unclear. In dermatomyositis, also, there are variations within the normal limits and occasionally marked abnormal fluctuations in the same case. Thus, Evans [54] described an example in which the values ranged from 8.7 to 14.5 mg. Marinesco [55] observed an instance in which the blood calcium was 16.8 mg., but this is unique. Petges [56] recorded an elevation in the calcium in the blood in cases of poikilodermatomyositis associated

52. Keil, H.: Relation Between "Systemic" Lupus Erythematosus and a Peculiar Form of Thrombocytopenic Purpura, Brit. J. Dermat. **49**:221, 1937.

53. Marinesco, G.; Draganesco, S.; Facon, E., and Buttu, G.: Studium eines Falles von Polymyositis haemorrhagica mit Purpura, Deutsche Ztschr. f. Nervenh. **143**:229, 1937. Schuermann.[3b]

54. Evans, P. R.: Case of Dematomyositis, Brit. J. Dermat. **49**:122, 1937.

55. Marinesco, G., in Brouardel, P., and Gilbert, A.: Nouveau traité de médecine et de thérapeutique, Paris, J. B. Baillière et Fils, 1910, vol. 38.

56. Petges, G.: Notions nouvelles sur la poikilodermatomyosite et processus voisins (Poikilodermatomyosite avec concrétions calcaires), Arch. dermat.-syph. de l'Hôp. St. Louis **5**:177, 1932.

with the deposition of calcium in the subcutaneous tissues. The significance of all these observations remains unclarified, and too much reliance should not be placed on these chemical studies as indicating an alliance between diseases such as dermatomyositis and scleroderma.

In cases of both systemic lupus erythematosus and dermatomyositis calcific deposits may occur in the subcutaneous tissues, while in rare instances of the latter disease the muscles may be similarly involved. The relation of these phenomena to the blood calcium is obscure, though it seems probable that they are unrelated in a direct sense; in any event, there is need for further investigation of the problem.

(*b*) Creatine and Creatinine Metabolism: In dermatomyositis creatine is excreted in pathologic amounts in the urine, with simultaneous diminution in the creatinine. This as well as other related phenomena appears to be dependent on the degree of muscular damage and as such is likely to be encountered in many other similar diseases, for example, trichinosis, pseudohypertrophic muscular dystrophy, myositis fibrosa and other myopathies. The subject need not be discussed further except to stress the point that such chemical disturbances merely indicate the occurrence of muscular disease and afford no clue as to the precise nature of the disease. It seems probable that similar changes will be found in the rare example of systemic lupus erythematosus accompanied by muscular atrophy, but there is need for further research to substantiate the point.

Preliminary investigations seem to indicate that lactic acid metabolism is not significantly altered in dermatomyositis, but the observations are too few as yet. In rare instances of this disease the content of uric acid in the blood has been observed to be elevated.

(*c*) Carbohydrate Metabolism: It has been observed that damaged muscles show a diminished content in glycogen, and that under such circumstances there may be an increased sugar tolerance. This phenomenon has not been studied adequately as yet in cases of dermatomyositis. It is interesting that there are on record a few examples of this disease in which the blood sugar content was much below the lower limits of normal,[57] but the significance of this finding remains to be evaluated.

(*d*) Sodium and Chloride Metabolism: As both conditions may occasionally simulate Addison's disease, it seems desirable to pursue studies relating to the metabolism of sodium, potassium and chloride. It appears, however, that a low sodium value in the blood is not pathognomonic of Addison's disease. Despite the claim of an occasional author, it can be stated confidently that neither systemic lupus erythematosus nor dermatomyositis has been shown, with reasonable certainty, to be

57. Randolph, C. C.: Calcinosis Universalis and Dermatomyositis, J. Pediat. 4:342, 1934.

related in any way to Addison's disease, and the same can be said of scleroderma. Too much reliance has been placed on superficial resemblances in the clinical picture; the postmortem material has been evaluated uncritically for the most part; few thorough chemical studies have been pursued, and undue stress has been laid on therapeutic tests of doubtful import. Reinvestigation of this phase of the subject seems in order.

4. *Serologic Data.*—In cases of systemic lupus erythematosus the blood often gives a positive Wassermann reaction or an anticomplementary reaction. This seems to be more than simple coincidence for the following reasons: 1. The incidence appears to be considerable, as I have encountered the phenomena in more than 10 cases of this disease and have data on several others. 2. The blood often gives an anticomplementary reaction on one or more occasions and may finally yield a positive reading. 3. With apparent improvement or temporary cure of an attack of the condition, the serologic reaction of the blood to the Wassermann test may become negative; under such circumstances a negative reaction may be regarded as a good prognostic sign, though there is, to be sure, great variability in the results of this test. When the Wassermann reaction is positive, the results range between 1 and 3 plus, rarely to 4 plus, and it is the rule to encounter wide fluctuations in successive reactions. Moreover, it is also relatively common to observe variations depending on the particular serologic technic employed; for example, the Wassermann test may be negative while the Kahn is weakly positive and vice versa. Many years ago Gennerich suggested that the positive Wassermann reaction obtained in cases of lupus erythematosus was caused by a lymphocytic "ferment" derived from enlarged lymph nodes observed commonly in this disease. The present knowledge would lead the investigator to expect that the factor responsible for these abnormalities would be found in the globulin fraction in the blood. Recently Coburn and Pauli,[57a] studying 2 classic examples of systemic lupus erythematosus with anticomplementary blood and increased globulin values in the serum, observed that the factor responsible for the anticomplementary reaction was in the globulin fraction; this observation seems significant as a preliminary step in the elucidation of the nature of the phenomenon. An occasional observer has also noted an increase in the globulin value in the serum,[58] and I have made the same observation in a few cases. There are, however, many instances of systemic lupus erythematosus in which this seems to be absent, and, contrariwise, there is no precise correlation between the serologic phenomena mentioned and the globulin values in the serum.

57a. Coburn, A. F., and Gutman, A. B.: Personal communications to the author.

58. Taussig, A. E.: Still's Disease with Hyperglobulinemia, J. Lab. & Clin. Med. **23**:833, 1938. Coburn and Gutman.[57a]

Not rarely in such cases of systemic lupus erythematosus treatment with antisyphilitic drugs has been employed, the results of such therapy being indifferent or even harmful. Furthermore I have observed an unusual instance of the disease, in which tests of the spinal fluid of a girl who also had atrophy of the optic nerve [59] resulted in a verified dementia paralytica type of colloidal gold curve; a single determination for globulin gave a moderately positive result. Neither in this case nor in the others with positive serologic reactions of the blood could syphilis be established as a cause. That syphilis may occur coincidentally in patients with systemic lupus erythematosus is to be expected in occasional instances; on the other hand, there are instances of true syphilitic eruptions on the face, especially those with unilateral distribution, in which the "superficial" variants of lupus erythematosus may be strikingly simulated, and these cases often defy the diagnostic acumen of the most expert. Finally, I have notes on 1 example of systemic lupus erythematosus in which the blood of the patient agglutinated itself spontaneously while the Wassermann reaction of the blood was 3 plus; in addition, a blood count revealed a fair number of myelocytes, so that leukemia was suspected. It follows, then, that each case must be individualized, with the understanding that a positive Wassermann reaction may sometimes complicate the clinical picture of systemic lupus erythematosus.

In cases of dermatomyositis the incidence of positive Wassermann reactions [60] seems to be small, and I have not met with any case illustrating this association. There are a few recorded examples of dermatomyositis in which syphilis was invoked as a cause.[61] Perusal of the protocols on these cases reveals that the diagnosis was based on doubtful clinical criteria in the era before the Wassermann test or on therapeutic tests that gave dubious results. In view of the rarity of such instances (nearly all were cases of polymyositis without cutaneous lesions), the spontaneous recoveries of persons with this disease and the possibility of a coincidental syphilitic infection, it seems fair to conclude that there are few, if any, cases of dermatomyositis in which syphilis has been definitely proved to be the cause.

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59. Goldstein and Wexler.[27] Records of the Mount Sinai Hospital.[28]

60. Schwarz, R.: Beitrag zur Aetiologie der Polymyositis, Frankfurt. Ztschr. f. Path. **25**:141, 1921. Milian, G.: Erythroedème myasthénique, Rev. franç. de dermat. et de vénérol. **10**:347, 1934.

61. Herrick, J. B.: Polymyositis Acuta, with Report of a Case Presumably of Syphilitic Origin (Myositis Syphilitica), Am. J. M. Sc. **111**:414, 1896. Lorenz, H.: Die Muskelerkrankungen, Vienna, A. Hölder, 1898, p. 227. Hoffmann, V.: Syphilis der Muskeln, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 17, pt. 3, p. 241.

C. PROGNOSIS

The prognosis for recovery, complete or incomplete, is grave in almost all authentic instances of systemic lupus erythematosus in which the patients have been followed for more than five years. The so-called cures that have been recorded concerned patients who experienced temporary improvement and were not observed long enough to warrant a precise opinion. It must, however, be admitted that this phase of the subject has not yet been thoroughly enough exploited to permit drawing of absolute conclusions. Thus, I have encountered cases in which the clinical course, which was finally fatal, ran far beyond the five year period from onset of constitutional symptoms referable to this disease.[52] It is not uncommon to encounter patients who show cutaneous lesions year after year, especially during the summer months, and in these patients the condition may go on for a long time before manifesting evidence of systemic involvement. Early in my observations I regarded evidence of renal involvement as indicating a fatal prognosis in the immediate attack of the disease, but this rule, while nearly always true, appears to have exceptions. Thus, I have several times observed more or less transient recoveries, at least in a clinical sense, of patients who manifested undoubted signs of disease in the kidneys; nevertheless, continued observation taught that these recoveries were only temporary. It is curious that in a few of these cases examination of the fundi showed swelling of the regions of the papillas, as described in a previous section in this paper. No conclusions can, however, be drawn from this combination of events, as occasional patients may, in the absence of such changes, experience sufficient improvement to permit the term "temporary recovery" to be applied to their condition. The reversal from a positive to a negative serologic reaction of the blood is interpreted in the same way as the aforementioned data.

On the other hand, I have pointed out in other publications that the temporary absence of detectable systemic manifestations indicates a good prognosis only in the immediate attack, for this may be followed, after variable periods, by a fresh exacerbation with lethal outcome. I have notes on 1 case in which the patient had discoid atrophic lupus erythematosus for about twelve years before exposure to ultraviolet rays caused generalization of the disease; postmortem examination revealed the typical findings of systemic lupus erythematosus. Such instances would lead one to believe that the disease may occasionally occur in a more benign form and that there may be patients, especially those seen in early stages before the supervention of constitutional symptoms, in whom the disease may either run a prolonged course or who may even recover completely. It is apparent that the subject is best studied by one who has access to material in a dermatologic dispensary and medical

wards. It is for this reason that I believe the last word on prognosis has not yet been spoken, though for the vast majority of patients showing evidence of systemic reaction death seems to be practically invariable. The causes of death in instances of this disease are numerous. Summarized briefly, they are: (1) bronchopneumonia arising from a superimposed infection, the swallowing of debris by patients with oral, pharyngeal or tracheal lesions and occasionally secondary infection of small infarctions in the lungs (closure of pulmonary vessels); (2) renal insufficiency; (3) a state of profound "toxemia" in which either the vascular lesions to be discussed later are relatively insignificant or absent, or the extent of pneumonic disease is apparently too slight to explain the death satisfactorily; (4) intercurrent bacteremia due to (*a*) the common aerobic bacteria, such as Streptococcus haemolyticus and Staphylococcus aureus and (*b*) tuberculous bacillemia with miliary tuberculosis; (5) cardiac failure, especially affecting the right side; (6) meningeal disease, and (7) combinations of the foregoing factors, etc.

The prognosis for dermatomyositis seems to be much better than for systemic lupus erythematosus, though it is still serious, as a mortality rate of over 50 per cent has been recorded.[3b] It must be stressed, however, that this is probably a conservative estimate, for in many instances dermatomyositis, like systemic lupus erythematosus, has shown itself to be a relapsing and recurrent disease. Nevertheless, there are cases in which the condition appears to enter a chronic phase or in which complete recovery apparently supervenes or in which the clinical picture is sooner or later succeeded by that of myositis fibrosa with its crippling effects. Thus, Weber and Gray observed a patient who remained cured for at least thirteen years. Weinberger [62] recorded an instance in which there was freedom from disease for nine years, followed by an attack that proved fatal. In Turner's third case [3a] the patient had the disease at the age of 5 years, with complete recovery; after a symptom-free interval of eight years there was a much severer recurrence which apparently entered a chronic phase of the disease. Blau [12] recorded an instance in which the first attack at the age of 14 years was interpreted as poliomyelitis; six years later there was a recurrence, and the clinical picture of myositis fibrosa was now well established. There are many other examples in which the patient was known to have had the disease for a decade or more, and it suffices for the present to take cognizance of the point. Throughout this presentation it has been noted that the clinical picture of the disease may begin with what seems to be systemic lupus erythematosus and that after a variable interval there appear the characteristic features of dermatomyositis. The cases of the myasthenic

62. Weinberger, M.: Ueber ein chronisch verlaufende Polymyositis mit Ausgang in progressive Muskelatrophie, Wien. med. Wchnschr. **83**:100, 1933.

form of lupus erythematosus (Gougerot) and of myasthenic erythredema (Milian), in some of which there was apparent cure, represent in all likelihood instances of ordinary dermatomyositis; the reasons for this view will become clear on consideration of the cutaneous manifestations and the clinical features of these conditions as well as a number of other syndromes, the names of many of which have now entered the phase of patronymic nomenclature.

The causes of death in cases of dermatomyositis are somewhat different from those in instances of systemic lupus erythematosus. Briefly summarized, they are: (1) bronchopneumonia chiefly due to paralysis of the small muscles in the pharynx, the intercostal muscles or the muscles in the diaphragm, as a consequence of which aspiration of material, infected or noninfected, is likely to occur (involvement of these small muscles is not necessarily accompanied by death, for in occasional instances temporary or more permanent recovery may take place; nevertheless, evidence of such paralysis is to be regarded apprehensively); (2) intercurrent complications, such as the invasion of the blood stream by Str. haemolyticus from a sacral decubitus sore; (3) cardiac failure, generally affecting the right side but occasionally affecting the left side as well, and (4) unexplained causes, such as "cachexia." Sudden death from suffocation is commonly encountered in patients with dermatomyositis as a result of marked involvement of the small muscles already mentioned, but this type of outcome is not rarely met with in patients afflicted with systemic lupus erythematosus; in most instances of the latter disease the cause seems obscure.

D. PATHOLOGIC DATA: CRITICAL ANALYSIS OF THE "VASCULAR CONCEPT" OF SYSTEMIC LUPUS ERYTHEMATOSUS AND DERMATOMYOSITIS

The data recorded thus far indicate that systemic lupus erythematosus and dermatomyositis, while often affecting the skin in somewhat similar fashion, display a predilection for certain parts of the body in a manner peculiar to themselves. Thus, in systemic lupus erythematosus the kidneys, heart, articulations and serous membranes are especially involved; in dermatomyositis, the muscular system. From time to time observers have hazarded the opinion that these organs are implicated chiefly through their respective blood supply and have accordingly grouped these as well as other conditions under the generic head of "diffuse vascular disease." Thus, in cases of systemic lupus erythematosus the major alterations may be observed in the small blood vessels, usually the capillaries, although the arterioles and venules, occasionally even the larger vessels, may also be affected. In cases of dermatomyositis the vascular changes, when encountered, seem to concern arterioles

somewhat larger (muscles), though usually smaller than those affected in periarteritis nodosa, while the capillaries (skin, muscle) are also commonly involved. If the unique case recorded by Talbott and his associates [63] is accepted as one of dermatomyositis, this instance would be, so far as I can ascertain, the only one in which the interlobular arteries in the kidneys were so strikingly affected. In view of the rarity of such alterations in dermatomyositis, it would seem wise to place this case to one side until the precise nature of this instance as well as that of the anatomic findings is fully established. In the discussion to follow I am less concerned with the histologic descriptions of the pathologic alterations than with the interpretations and conclusions drawn from them.

There is, in my opinion, little justification for classifying these diseases as genuine examples of "diffuse vascular disease," except occasionally, for this designation carries with it at least two important implications: 1. It presupposes that the vascular changes are universal, easily recognized and fairly constant; it is my belief that this is actually not the case. 2. It allows for confusion with other conditions in which the vascular tree also apparently bears the brunt of the process, so far as pathologic examinations are concerned; to mention only a few, arteriosclerosis (arteriolosclerosis), periarteritis nodosa and typhus fever.[64] Indeed, there is reason to believe that the vascular alterations observed in cases of systemic lupus erythematosus and dermatomyositis explain the clinical features far less satisfactorily than, for example, in cases of periarteritis nodosa. The term "diffuse vascular disease," while therefore possessing some utility, has little diagnostic value per se; its use is the equivalent of saying that a patient has purpura, without attempting a finer clinical differentiation. A similar criticism applies to the use of the term "mesenchymal disease," which represents only an expedient way of expressing an antomic concept. But the problem does not end with the qualification of these terms, for soon several disturbing questions arise:

63. Talbott and others.[22] Footnote 23.

64. Baehr, G., and Sacks, B.: The Occurrence of Glomerulonephritis in Association with Verrucous Endocarditis, Proc. New York Path. Soc. **23**:64, 1923. This is an example of how far astray the concept of "diffuse vascular disease" ("endotheliotropic virus") may lead. This term is applied not only to ordinary glomerulonephritis, but also to 3 cases that are now believed to be examples of rheumatic fever. In the same communication, reference is also made in a similar sense to 2 instances of atypical verrucous endocarditis; the 3 aforementioned cases were detailed by Dr. E. Libman in a letter written to Dr. L. Gross, chairman of the Laboratory Committee of the Mount Sinai Hospital, dated Feb. 10, 1936, and Dr. L. Gross, in a personal communication, stated that these cases were definite examples of rheumatic fever to be reported again by him in detail at some future time. The vascular lesions described in this paper were originally found by B. Sacks (E. Libman: Letter written to Dr. L. Gross, chairman of the Laboratory Committee of the Mount Sinai Hospital, dated Feb. 10, 1936).

1. *Systemic Lupus Erythematosus.*—A. Can one speak of lesions pathognomonic of this disease? It is my belief that, on the whole, this question may be answered in the negative. The "wire-loop" lesions occurring in the glomeruli of the kidneys in cases of systemic lupus erythematosus may be regarded as highly characteristic. Interestingly enough, I have encountered them in a case of this disease accompanied by marked wasting of muscles in the limbs and other parts. In another publication [2b] I have briefly discussed the importance of these alterations in the kidneys and there expressed the view that the "vascular concept" does not explain every phase in the disease process in systemic lupus erythematosus. The "wire-loop" lesions may be regarded as a secondary expression of a disease the cause or causes of which still remain to be determined, though certain precipitating factors are known, for example, sunlight. The evidence compiled thus far appears to indicate that these changes are "toxic," occurring in patients with an unstable vascular system. Beyond this view, which is of course restricted in its scope, it seems unwise to go at present. Yet, despite these limitations, the vascular lesions in the kidneys have had, and still enjoy, a definite importance for: 1. They are often the earmark of systemic lupus erythematosus, and fewer cases of this sort would have been overlooked or remained buried in the records had the possible significance of these alterations been appreciated, for example, prior to 1930; [49] for it was by the correlation of these vascular lesions (originally as "hyaline thrombi") with the dermatologic and internal medical aspects that I was enabled in 1930 to arrive at a unified clinicopathologic conception of systemic lupus erythematosus.[65] 2. Their occurrence permits the pathologist to ally, at least temporarily, certain obscure conditions that at present defy precise classification. In doing this, the pathologist must not forget the clinical aspects, for such lesions or similar ones may be encountered in association with various other diseases, such as eclampsia, mycosis fungoides, "hyperergic inflammation" and probably other conditions. A concept based alone or chiefly on the renal lesions, without regard to the remainder of the clinical picture, would be one sided. Thus, in the days before the clinical features of systemic lupus erythematosus were sufficiently appreciated, the lesions in the kidneys, especially those accompanied by some degree of focal necrosis or marked hyalinization, were regarded as allied to the somewhat similar findings associated with subacute bacterial endocarditis or even healed subacute bacterial endo-

65. Keil, H.: Communication to the Libman Fellowship Foundation, Feb. 5, 1931. Libman, E.: Personal communication to the author, Nov. 22, 1931; personal communication to Dr. L. Gross, Chairman of the Laboratory Committee of the Mount Sinai Hospital, Feb. 10, 1936. Gross, L.: Personal communication to the author, Sept. 4, 1937.

carditis. On the basis of resemblances in appearance, which may be considerable, it was concluded that the lesions in cases of systemic lupus erythematosus are embolic. While this may possibly be true in the case of subacute bacterial endocarditis, there is adequate evidence that appears to contradict the application of such a belief to systemic lupus erythematosus.

Similarly, the vascular lesions reported as occurring in the heart and other structures in systemic lupus erythematosus are probably not pathognomonic of this disease, for similar or even identical changes may be encountered in occasional examples of rheumatic fever [64] and other conditions. The perivascular fibrosis observed sometimes in the spleen is probably also not a specific finding.

B. Are the vascular lesions always present in cases of systemic lupus erythematosus? It seems probable that such alterations are found in a large percentage of typical instances of systemic lupus erythematosus, but there are cases in which assiduous examination of the kidneys, for example, may fail to reveal these changes or in which their intensity and distribution hardly parallel the severity of the clinical features. In other words, there is great variability in the degree of severity and distribution of the lesions not only in the kidneys but also in other parts of the body, including the skin; the vascular alterations considered to be characteristic may be insignificant in extent and distribution, minimal or even altogether wanting. Mallory,[66] who has made a thorough study of the pathologic picture of this disease, concluded that there is no constant type of vascular lesion, and, moreover, he was able to find the "wire-loop" lesions in only one-half the cases or less.

Does the absence of "hyaline thrombi" in the skin mean that the condition under consideration is not systemic lupus erythematosus? An occasional case has been reported in the literature as showing this change,[5] and I can substantiate this point on the basis of 2 additional instances. These findings are, however, uncommon, and I have several times seen fragmented edematous collagenous bundles confused with them; moreover, study of serial sections and prolonged search are often essential to the discovery of them. It is probable, therefore, that too much reliance should not be placed on alterations of this sort, which, moreover, probably occur in other diseases as well. The pathologic diagnosis of systemic lupus erythematosus may be suggested by biopsies of skin on the basis of certain combinations of changes that will not be discussed here. That analogous alterations may often be seen in cases of dermatomyositis is not surprising when one considers the similarities

66. Disseminated Lupus Erythematosus, Cabot Case 24201, New England J. Med. **218**:838, 1938; Acute Disseminated Lupus Erythematosus, Cabot Case 24341, ibid. **219**:273, 1938.

in the structure of the eruptions. In any event, it seems doubtful whether one can speak of pathognomonic changes in the blood vessels as observed in these cases.

Of what importance is it to realize the limitations in such studies? There are instances in which, on the basis of similarities in vascular lesions, an alliance between diseases has been or will be advocated. Thus, Volk's [67] case has been cited in several reports as an example of periarteritis nodosa occurring in association with systemic lupus erythematosus; yet critical examination of the data reveals that the clinical features were entirely consistent with the diagnosis of systemic lupus erythematosus, while the criteria for the diagnosis of periarteritis nodosa were doubtfully fulfilled. Likewise, the occasional observation of certain types of vascular changes in the vessels of the kidneys in patients with scleroderma, for example, does not warrant, on this basis alone, an alliance between this disease, systemic lupus erythematosus, periarteritis nodosa, dermatomyositis and other such conditions. Here again, the clinical features and the collateral factors must be considered closely. The concept of "hyperergic inflammation" rests on similar grounds, and one has but to read the various reports concerned with this pathologic phenomenon to realize the disparity in diseases assembled under this head. The observation of "reticulosis" in a lymph node in a person with systemic lupus erythematosus was once made the basis of a theory on Still's disease or Felty's syndrome, and an interesting phenomenon, hardly pathognomonic per se, constituted the cornerstone for the interpretation of a case that presented the typical clinical features of systemic lupus erythematosus.[49]

Friedberg, Gross and Wallach [7] contributed an outstanding study on what they called nonbacterial thrombotic endocarditis, differentiating it from other varieties of endocarditis, especially atypical verrucous endocarditis and rheumatic heart disease. It appears, however, that nonbacterial thrombotic endocarditis may occur in association with many other pathologic conditions as well as superimposed on other types of endocardial disease. Beyond the observation that such verrucae may be confused with those observed in other conditions, it seems difficult to see how this finding could be used as a means of differentiating diseases; its very universality would seem to militate against such a view. Furthermore, it is my belief that the occurrence of nonbacterial thrombotic endocarditis would not eliminate the diagnosis of systemic lupus erythematosus, even if it were not superimposed on the more characteristic atypical verrucous endocarditis. In any event, knowledge of this type of endocarditis, the pathogenesis of which is still obscure,

67. Volk, R.: Periarteritis nodosa bei einem Lupus erythematodes chronica cum Exacerbatione, Dermat. Ztschr. **53**:682, 1928.

is important, if only to help one avoid confusing it with other diseases, for example, rheumatic fever and subacute bacterial endocarditis.

C. Another disturbing question relates to instances in which the post-mortem examination fails to reveal the changes regarded as characteristic of systemic lupus erythematosus. Does the absence of such alterations eliminate this diagnosis? It is my belief that there are occasional cases in which the clinical features are clearcut, yet in which the anatomic changes to be expected are lacking or hardly adequate to explain the entire clinical course. For example, I have observed an instance of this disease in which apparently nothing significant was observed at autopsy, except subacute pneumonia; it seems hardly likely that this finding, which was indeed the chief cause of death, could explain adequately the occurrence of a widespread eruption, accompanied by articular pains and a clinical picture that lasted several months. Again, the case recorded by Goldstein and Wexler [27] is another in point. Here the only pathologic alteration of note was observed in the eyes post mortem, and it seems hardly likely that this could explain the rapidly fatal course and the degree of "toxemia" shown by the patient. It is for this reason, among others, that the primary nature of the vascular lesions seems doubtful. It must therefore be concluded that there are examples of this disease in which the clinical aspects apparently assume greater diagnostic importance than the pathologic findings and in some instances may even override positive changes of more or less doubtful significance. These data are therefore in agreement with the views propounded by Dr. Soma Weiss.[66]

2. *Dermatomyositis.*—In cases of dermatomyositis pronounced vascular alterations seem to be less commonly encountered, and some observers have therefore suggested that this disease be classified under two heads: (*a*) conditions showing changes in the blood vessels, and (*b*) those free from such alterations. When present, the vascular lesions apparently possess a significance somewhat similar to that in cases of systemic lupus erythematosus. In agreement with the clinical features, the pathologic changes are found chiefly in the muscular tissues. Many disturbing questions arise in the study of these cases!

A. Are these vascular lesions, when present, pathognomonic of dermatomyositis? Two types of changes in the blood vessels have been considered as especially significant: 1. Capillary dilatation in which these vessels teem with blood elements. This appearance has been stressed by some as the primary change in the disease, and for these observers the term angiomyositis seems to express best the fundamental nature of this condition. Whether this appearance is indeed representative of the initial disturbances in this disease has not yet been definitely determined, but it seems fair to note that such changes may be

encountered as a banal pathologic phenomenon in other conditions as well and are therefore difficult to assess. 2. Various other types of vascular damage. Changes ranging from subintimal involvement with its secondary effects to a true "necrotizing arteriolitis," in which the brunt of the process is apparently borne by the media or other portions of the vascular parietes, have been recorded as occurring in cases of dermatomyositis. Fahr has attempted to ally these changes with those seen in association with periarteritis nodosa, using the latter term in its broadest pathologic connotation. It is my belief that, while there may be similarities in the pathogenesis of such vascular alterations, nothing more than this can be concluded. With a few exceptions, it can be said that knowledge of the clinical picture is essential before claims can be made for the specificity of such vascular lesions.

B. Are these vascular changes always found in typical cases of dermatomyositis? There are many examples of this disease in which the extent of the damage to the blood vessels seems relatively insignificant in comparison with the degree of muscular involvement. It must be admitted, however, that this observation cannot be judged rigorously in the absence of serial sections of muscle or an examination of large portions of it, for it is conceivable that significant vascular lesions may be overlooked owing to insufficient search. Yet even thorough post-mortem studies indicate clearly that in many instances the muscular changes appear to be disproportionately severe as compared with those seen in the blood vessels, and there are examples of this disease in which the latter alterations seem altogether insignificant or completely absent. For these reasons some investigators believe that the same etiologic agent may attack both the muscles and the blood vessels either concurrently or independently, and for many of these observers it seems more likely that the muscles are primarily affected.

It becomes evident, then, that the nature of the muscular alterations, whether primarily, secondarily or concurrently involved, whether degenerative or inflammatory, still admits of considerable debate. Further, the degenerative changes in the muscles appear to be even less specific than the vascular changes described, and, indeed, the whole subject of the pathologic anatomy of the myopathies is in want of fresh investigation. In the average case of dermatomyositis examination of muscular tissue generally reveals widespread alterations in the parenchyma, these being easily recognized. Yet numerous reports on other diseases, for example, scleroderma, show that simple atrophy, atrophy from disuse, atrophy from mechanical pressure and other types of atrophy have been regarded as identical with the changes occurring in dermatomyositis. What makes the problem especially difficult is the observation that the alterations in the muscles may be considerably influenced by all sorts of secondary phenomena, and this occurs not only

in dermatomyositis but in many other diseases as well. It seems that here again there must be a close clinicopathologic correlation until such time as better criteria are evolved. As long ago as 1888 Jacoby,[13] in comparing the muscular alterations in his case of polymyositis with those associated with typhoid fever, remarked that even if the results of microscopic examination were identical, "we could not be justified in considering the processes as clinically analogous." The difficulties in evaluating the nature of muscular pathologic changes become manifest on study of the excellent monograph written by von Meyenberg.[68] It is probable that the muscles are more often affected in a wide variety of diseases than is generally suspected, and it is essential to examine this tissue under manifold conditions. These alterations need to be studied in relation to the clinical features, and perhaps then more information will be forthcoming in regard to the nature of these changes, the most favorable sites for removing specimens for biopsy and the diagnostic value of such examinations and other matters. The occasional observation of "reticulosis" and of a chronic granulomatous change about blood vessels are interesting findings to which, however, undue etiologic significance must not be too readily attached. It is my belief that at the present time the clinical aspects are of greater importance in the classification of examples of this disease, but in all instances a clinicopathologic correlation seems not only desirable but also essential.

In the discussion of these diseases only brief mention has been made of a number of phenomena which appear to be of "vasomotor" origin and for which it seems unlikely that there will be found anatomic changes sufficiently marked to characterize these symptoms. These manifestations (for example, the pronounced sweating occasionally associated with dermatomyositis) seem to require physiologic studies for clarification.

SUMMARY

This study is concerned with a comparative analysis of the essential clinicopathologic features presented by systemic lupus erythematosus and dermatomyositis. Among the clinical phenomena encountered in both diseases are fever, pains generally regarded as articular, similar cutaneous and oral lesions, sensitivity to sunlight, Raynaud-like symptoms, lymphadenopathy, splenomegaly, leukopenia, tendency to purpura, alopecia of the scalp, sterile cultures of blood, muscular involvement and renal disease. At times both diseases may also run an afebrile course, and the clinical picture may occasionally be dominated by what may be called the sequelae of these conditions. Despite these

68. von Meyenberg, H.: Die quergestreifte Muskulatur, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie. Berlin, Julius Springer, 1929, vol. 9, pt. 1, p. 299.

similarities and the occasional overlapping of features, the average typical example of each disease runs a fairly distinctive course. The main body of the paper is devoted to an analysis of the differences in the clinicopathologic attributes. These are studied under the following headings: (1) age, sex and seasonal incidence, (2) cutaneous lesions, (3) disease in the muscles, (4) involvement of subcutaneous tissue, (5) articular involvement, (6) renal disease, (7) ophthalmoscopic observations, (8) cardiac involvement, (9) disease in the serous membranes, (10) anomalies of the lymph nodes, (11) involvement of the spleen, (12) disease in the liver and (13) involvement of the brain. Certain laboratory data are also compared. Likewise, differences in the prognosis are briefly discussed. Finally, the pathologic data thus far available are subjected to a critical examination with respect to their significance for diagnosis, and an effort is made to expose some of the many problems encountered in the evaluating of such observations.

ARTERITIS OF THE TEMPORAL VESSELS

REPORT OF A CASE

JAMES M. BOWERS, M.D.
SEATTLE

During the past few years an occasional case has been observed of an inflammatory condition selectively involving the temporal arteries which differs clinically and pathologically from the conditions classed under the headings of thromboangiitis obliterans, periarteritis nodosa and rheumatic arteritis. Biopsy shows that the attack of the invasive agent is centered on the medial coat, producing moderate necrosis with hemorrhage at times, and that destroyed areas are replaced with granulation tissue in which numerous giant cells are invariably present. All coats may be involved, which results in intimal thickening and round cell infiltration of the adventitia, and the process may extend to tissues around the arteries. The lumen of the vessel may be closed by thrombosis. Formation of small aneurysmal sacs arising in the media is not observed in this disease as it is in periarteritis nodosa.

The cause of this clinical syndrome is unknown, and for want of better nomenclature it is called merely arteritis of the temporal vessels. Cultures of material from the media of a number of resected temporal arteries, blood cultures, agglutination tests for typhoid, paratyphoid, undulant fever and tularemia, examination of the spinal fluid, inoculation of animals and the use of special staining methods for microorganisms of syphilis and tuberculosis have failed to yield definite information of the specific causative agents. Roentgen examination of the head, thorax and spinal column, as well as urinalysis, has given essentially negative results.

The disease affects both sexes and occurs usually in persons past 60 years of age, often in persons with signs of arterial hypertension and arteriosclerosis. The illness lasts about five or six months, with some tendency to relapse but with eventual complete subsidence. It is well known for its nonfatal outcome in contrast to periarteritis nodosa, which generally produces fatal results within a year. The entity is characterized by periarteritis and arteritis of the temporal vessels. Other vessels have been thought to be involved, such as the cerebral,

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retinal and radial arteries. In the case to be reported here it was rather obvious clinically that the occipital arteries were inflamed at the same time.

The most outstanding complaint has been that of dull, throbbing headache which is usually worse at night. Also, there appear fever, night sweats, poor appetite, loss of weight and strength, anemia, weakness and mild leukocytosis; these symptoms may precede by several weeks the signs of inflammatory involvement of the temporal arteries. In time the vessels become enlarged and tortuous and are surrounded by areas of hyperemia. Small nodules may be seen or felt over the main branches or the smaller ones, and pulsations may be only partly absent or entirely absent, according to the patency or the degree of occlusion of the lumen.

The condition was first recognized as a distinct arterial entity at the Mayo Clinic in the spring of 1931, approximately eight years before the reading of this paper. The observers, Horton, Magath and Brown, published a report of 2 cases, in the winter of 1932 [1] and the spring of 1934.[2] MacDonald and Moser [3] reported a similar case in the spring of 1937; Horton and Magath [4] reported a total of 7 cases (observed at the Mayo Clinic) in the fall of 1937 and mentioned a complete report of another case which they had received from three physicians in Uruguay. One year prior to the time of this report, two physicians of London, England, Jennings [5] and Bain,[6] published their findings in 3 cases. Recently Horton stated in a personal communication to me that he had observed 3 additional cases in the past six months. The following case was first recognized by me as one in which the signs and symptoms of arteritis of the temporal vessels were apparent seventeen months ago. It is the sixteenth case of this condition to be placed on record.

REPORT OF CASE

History of Illness.—A married white woman aged 65 years was seen in my office Sept. 18, 1937. She was a former music teacher whose husband was unemployed. She was neurotic and hypertensive. She had been referred to me

1. Horton, B. T.; Magath, T. B., and Brown, B. E.: An Undescribed Form of Arteritis of the Temporal Vessels, Proc. Staff Meet., Mayo Clin. **7**:700-701 (Dec. 7) 1932.

2. Horton, B. T.; Magath, T. B., and Brown, B. E.: Arteritis of the Temporal Vessels: A Previously Undescribed Form, Arch. Int. Med. **53**:400-409 (March) 1934.

3. MacDonald, J. A., and Moser, R. H.: Periarteritis and Arteritis of the Temporal Vessels: A Case Report, Ann. Int. Med. **10**:1721-1726 (May) 1937.

4. Horton, B. T., and Magath, T. B.: Arteritis of the Temporal Vessels: Report of Seven Cases, Proc. Staff Meet., Mayo Clin. **12**:548-553 (Sept. 1) 1937.

5. Jennings, G. H.: Arteritis of the Temporal Vessels, Lancet **1**:424-428 (Feb. 19) 1938.

6. Bain, C. W. C.: Arteritis of the Temporal Arteries, Lancet **1**:517 (Feb. 26) 1938.

by a general practitioner, who considered her completely invalidized by pains about the head which she had had for eleven weeks. These were thought to be due to arterial hypertension and known to have been present for ten years. They were ascribed to exhaustion brought on by the unwelcomed presence of a relative in the household.

The pains in the head had been constant, dull and throbbing, usually disturbing the patient's sleep at night. For the first five weeks they were limited to the occipital region, but in the past six weeks they had been present in the temples. They were not associated with effort or posture. They had been so severe as to cause almost complete loss of willingness to eat, and her nourishment for some time had consisted of two slices of bread a day, which had resulted in a loss of 15 pounds (6.8 Kg.) in weight. The tongue had been red and burning, and she had noticed swelling in the region of the salivary glands. She felt faint, weak and at times feverish. She was admitted to the hospital on September 20.

Personal History.—The patient's father and mother died in old age. A brother died at 50 years of age of a general physical breakdown, and a sister succumbed to carcinoma at 55 years of age. The patient's husband, a jeweler, had been unemployed for many years. Her two children were instructors in the field of art.

The patient had suffered intensely from dysmenorrhea and migraine in youth and had been traumatized during parturition. At the age of 43 years a right nephropexy, an appendectomy, a partial oophorectomy and suspension of the uterus had been performed. These operations had been followed shortly by removal of a tumor from the right cheek and removal of a urethral caruncle. The menopause had taken place at the age of 50, without untoward symptoms.

Two years before she was seen by me, the patient had been examined by an internist, who recorded a blood pressure of 234 systolic and 112 diastolic. He found the peripheral arteries generally thick walled and tortuous and could find no pulsation in the left dorsalis pedis artery. There was severe trichophytosis on the toes of the left foot. A toe nail was removed, and the patient was advised as to the care of chronic nervous exhaustion and constipation, for which she had previously interviewed several physicians. One month later she wrote that she was no better, was tender in most parts of her body and ached from the waistline down.

Physical Examination.—The patient was intelligent. She showed some dehydration, emaciation and pallor. She was nervous and tense. Immediately before her admission to the hospital her blood pressure was 160 systolic and 110 diastolic. With rest in bed and the use of sodium phenobarbital it rapidly declined to as low as 120 systolic and 70 diastolic and remained within normal range in the two determinations made daily. The temperature varied from 97 to 101.4 F. and the pulse rate from 76 to 92 per minute; the respiratory rate was stationary at 20 per minute.

Both anterior branches of the temporal arteries, but especially the left, were prominent from a point just above the temporomandibular joint for a distance of about 7 cm. They were somewhat thickened and tortuous, of irregular caliber and without pulsation throughout, but they were not nodular. The tissue around the central portion of the left vessel was hyperemic, and the preauricular glands were moderately enlarged. On questioning, the patient always designated the region of these arteries as the site of her pain of the past few weeks, especially at night. At various times they were exquisitely tender, and after biopsy material had been taken the swollen and reddened proximal end of the left vessel was especially tender.

The pain had been located formerly in the occipital arteries and was excruciating. Later there was pain in the anterior branches of the temporal arteries, and, although pain had largely disappeared from the former site, the occipital arteries were still tender, tubular and thick walled. Their caliber was regular, and no nodules were present, nor could any satellite glands be palpated. These arteries were likewise involved in an inflammatory process for a distance of about 7 cm. from a point above their emergence into the occipital triangle. No other peripheral vessels were similarly involved.

The extraocular movements of the eyes were normal. The pupils were small but reacted normally to light and accommodation. The media were clear, and the retinal arterioles showed sclerotic changes, but neither hemorrhage in the fundi nor papilledema was present. The nasal spaces and mucous membranes were normal, and there was no evidence of infection of the paranasal sinuses to inspection or transillumination. The ears were normal. The tongue was bluish scarlet, with atrophy of the marginal papillae. The tonsils were atrophic and without infection. The pharynx, nasopharynx and larynx were normal. The patient was endentulous.

The neck was normal. The breasts were normal. The heart was not grossly enlarged, and there was slight accentuation of the aortic second sound. The lungs were normal. The liver and spleen were not palpable, and no mass was felt in the abdomen. Vaginal and rectal examinations revealed no abnormality. The reflexes were intact and normal throughout. Pulsations in the dorsalis pedis and posterior tibial arteries on the right were only moderate; on the left they were absent.

Laboratory Observations.—The urine showed a trace of albumin. The concentration of hemoglobin was 80 per cent (Dare). The red blood cells numbered 4,070,000 and the white blood cells 12,450 per cubic millimeter, with neutrophils 89 per cent and lymphocytes 11 per cent. The Wassermann reaction of the blood serum was negative. The sedimentation rate of the red blood cells was 28 mm. in a sixty minute period (Wintrobe). The bleeding and clotting times and the platelet count were normal. Agglutination tests for undulant, typhoid and paratyphoid A and B fevers gave negative results. The value for urea nitrogen was 18 mg., that for creatinine 1.8 mg., that for nonprotein nitrogen 54 mg. and that for sugar 111 mg. per hundred cubic centimeters of blood. The carbon dioxide-combining power was 52 volumes per cent. Analysis of the gastric contents showed a value for total acidity of 38 and for free hydrochloric acid of 16, in terms of cubic centimeters of one-tenth normal sodium hydroxide.

Roentgen and Electrocardiographic Studies.—Roentgenograms of the paranasal sinuses were normal. A roentgenogram of the chest showed mild left ventricular hypertrophy, aortic dilation and tortuosity and mild fibrosis throughout both lung fields. Fluoroscopic and roentgen examination of the gastrointestinal tract after a barium meal revealed no abnormality. An electrocardiogram revealed a heart rate of 80 per minute, sinus arrhythmia, left axis deviation and mild myocardial damage.

Treatment.—The patient's total stay in the hospital amounted to four weeks. The first week was devoted to combating dehydration and undernourishment, to relief of pain and to a search for the cause of her profound discomfort. It was difficult for the patient to lay her head on a pillow on account of tenderness over the occiput; the pain in the temples was excruciating. She insisted that her suffering was not due to elevated blood pressure, renal disease, infection of the paranasal sinuses or gastrointestinal disturbances.

Potassium iodide and dicalcium phosphate were administered orally, concentrated liver extract and vitamin B_1 parenterally and sodium iodide, sodium salicylate and iron cacodylate intravenously. These gave little or no relief. The patient received some comfort from the frequent use of codeine sulfate and sodium phenobarbital administered hypodermically. Nourishing fluids were given intravenously, and eventually the caloric intake became satisfactory.

Because of fever, leukocytosis and designation of the anterior branch of the left temporal artery as the site of greatest discomfort, a diagnosis of subacute arteritis was made after one week in the hospital, and a segment of the vessel was removed for cultural purposes and for examination.

Biopsy and Pathologic Report.—With the region under local anesthesia an incision was made over the middle portion of the anterior branch of the left temporal artery, and a segment of the vessel, measuring about 2 cm., was removed (fig. 1). A culture was made of material from the tissue. Grossly, the tubular

Fig. 1.—Site of removal of the biopsy specimen. A small segment was taken from the anterior branch of the left temporal artery. Note that the artery is thickened and tortuous, with an irregular caliber.

piece of tissue was 1.5 cm. in length and 0.3 cm. in diameter. Microscopically, sections of the artery revealed variable degrees of chronic inflammation (figs. 2 and 3), and the intimal lining was extremely thinned. There was an organized thrombus which occluded the lumen except for a narrow crescentric channel. In the media there was marked infiltration of mononuclear cells, with frequent neutrophilic and an appreciable number of eosinophilic polymorphonuclear cells. Granulation tissue was present throughout. The adventitia was only mildly involved in the inflammatory process. The diagnosis was chronic arteritis. Cultures made on blood agar plates from the specimen removed from the temporal artery yielded a growth of gram-positive cocci in clusters.

Subsequent Course.—The area around the distal end of the severed artery became hyperemic and tender. However, the patient in a short time commented on her delight in the relief from severe pain at the site of removal of the biopsy specimen; presumably this relief was due to interruption of the pain pathway of

the sympathetic nervous system. During the remainder of her sojourn in the hospital the patient continued to improve. The temperature gradually subsided, until in three weeks it was nearly normal. She was able to rest and sleep better. Her intake of food soon amounted to 2,000 calories per day. Peculiarly enough, the presence of residual pain was noticeably affected by the intramuscular administration of vitamin B_1. The daily supply of this vitamin in amounts ranging from 500 to 2,000 international units afforded marked relief, and trial withdrawals repeatedly permitted the return of the pain within twelve to sixteen hours.

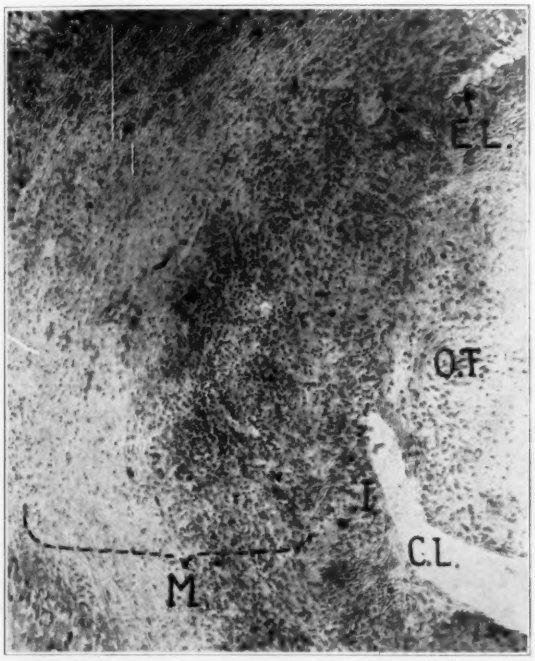

Fig. 2.—Low power photomicrograph of a cross section of the temporal artery. *M.*, the media, showing a vast amount of cellular infiltration, necrosis and granulation tissue. *E. L.*, the internal elastic membrane. *I.*, the intima, somewhat thinned. *O. T.*, an organized thrombus. *C. L.*, the crescentic lumen.

Follow-up.—The patient left the hospital October 17, and during the next six weeks she was seen several times. She remained constantly in bed for the first two weeks; this was followed by graduated intervals of sitting in a chair and of walking short distances. Her temperature declined to a normal level, her intake of food remained reasonably good. On November 17 her blood pressure was 138 systolic and 94 diastolic, and she had a feeling of slight increase in strength. Vitamin B_1 had been injected intramuscularly twice a week. Parenteral administration of tissue extract and oral administration of iron were ordered.

The incision over the left superficial temporal artery healed quickly, and there was rapid subsidence of signs and symptoms of inflammation in both superficial temporal arteries. The left occipital artery was normal to palpation and gave no distress, but the right one was occasionally causing a dull ache, especially at night, and was still thick walled and tender. However, in two weeks these symptoms responded to palliative and supportive treatment.

On Jan. 19, 1938, after prolonged worry over financial affairs, she noticed a return of cardiorenal symptoms on a hypertensive basis. Her blood pressure was 220 systolic and 110 diastolic. However, she was entirely free from pain over

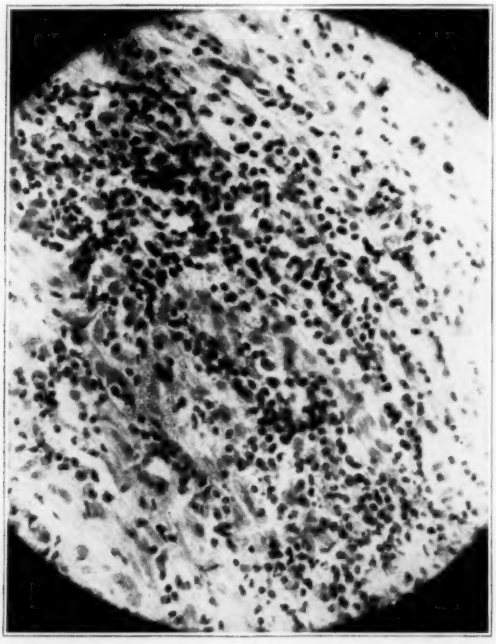

Fig. 3.—High power photomicrograph of a cross section of the media of the temporal artery. There is evidence of marked infiltration with neutrophilic and eosinophilic polymorphonuclear and mononuclear cells and granulation tissue.

the courses of the temporal and occipital arteries. Sedatives were supplied, but six weeks later the condition was about the same and the blood pressure still markedly elevated. During the latter part of April she felt much more comfortable, and there was considerable lessening of the hyperpiesis.

Then, one year after the patient was first seen by me (September 1938), she appeared in my office, hardly able to walk or talk because of profound weakness. The mouth was dry and the tongue red and coated; the abdomen was distended with gas, and the extremities were cold. The pulse rate was 92 per minute, and the blood pressure was 230 systolic and 120 diastolic. She admitted that she had eaten little food and had worried a great deal for several weeks. Three days

later she was readmitted to the hospital on account of vomiting and exhaustion. She sank slowly into a fairly deep coma which lasted five days. The muscles of the extremities were somewhat spastic, and she was restless in bed even though she was unconscious. The urinary bladder and the rectum were incontinent; eventually it was necessary to empty the bladder by catheter. There was no inequality or unusual change in the reflexes of the extremities. The pupils were normal in size. Fever was absent. When the pulse became feeble it was necessary to digitalize the patient. No localized inflammation of the peripheral arteries was obvious. On admission the blood pressure was 230 systolic and 120 diastolic, but under the influence of barbiturates it rapidly dropped to a normal level.

Urinalysis gave essentially negative results. The initial blood count showed mild leukocytosis and eosinophilia. Hypochloremia was present until sodium chloride was supplied by infusion. The alkaline reserve and the concentration of blood urea nitrogen were normal. Examination of the spinal fluid was not performed. The value for "fasting blood sugar" was 183 mg. per hundred cubic centimeters, but with the daily administration of 15 units of protamine zinc insulin hypodermically it became normal. Dextrose in saline solution was given intravenously, and eventually 100 Gm. of carbohydrate was fed orally each day. Finally, after the evidence of disturbance of the carbohydrate mechanism had disappeared, the insulin was discontinued and the patient was placed on a general diet.

The patient rallied from her extreme weakness, with definite and fairly rapid improvement in color, hydration, weight and strength. She suffered from vertigo for several weeks, and an otologist concluded that the hyperirritability of the labyrinths was on an arteriosclerotic basis. An oculist reported moderate sclerotic changes in the retinal arterioles. Recovery was satisfactory enough within six weeks to permit the patient to leave the hospital. Again she remained in bed, most of the time at home, for a long period. Even though her blood pressure had risen to its previous high levels, she showed many signs of improvement in health, which was partly due to her attempt to suppress worry and to partake of a better diet.

Comment.—My final opinion as to the cause of the coma was that it might have been a cerebral vascular mishap, the exact mechanism of which, however, was not apparent to me. Obviously, whatever took place was a complication or a sequela of arterial hypertension and arteriosclerosis, just as the previous occurrence of inflammation of the temporal arteries probably can be considered an aftermath of the same conditions. The same form of arteritis that afflicted the temporal vessels may have involved the cerebral vessels.

There is presumably no specific treatment for the disease. In this case, before a biopsy specimen was taken, narcotics and sedatives were frequently employed to give relief from pain. Administering vitamin B_1 parentally and sodium iodide, sodium salicylate and iron cacodylate intravenously had little or no effect. The patient noticed immediate comfort after removal of a moderate-sized segment of the inflamed artery, which was maintained by injection of considerable amounts of vitamin B_1 until healing took place.

SUMMARY

A case of inflammation of the temporal arteries is presented. For a considerable period before diagnosis the associated headache was attributed to severe arterial hypertension. Undoubtedly, the occipital arteries were involved in a similar inflammatory process at the same time. Nine months after the subsidence of signs and symptoms, the patient suffered a cerebral vascular mishap, which probably was due to arteritis of the cerebral vessels, of the same nature. Interruption of the pain pathway of the sympathetic nervous system after resection of an arterial segment and injection of vitamin B_1 produced relief from pain. Many points in favor of designation of this condition as a separate entity of arteritis, especially of its distinction from periarteritis nodosa, may be found in the reports of the 16 cases now on record.

BODY BUILD AND HYPERTENSION

S. C. ROBINSON, M.D.
AND
MARSHALL BRUCER, S.B.
CHICAGO

Thus far there has been no conclusive proof in the medical literature that there is a correlation between body build and blood pressure. There are many authors who have stated with considerable positiveness that there is no relation. Bauer [1] and Braun [2] observed no characteristic build among hypertensive persons, and Hay [3] stated that both thin persons and those of the sthenic habitus are susceptible to hypertension. Alvarez and Stanley [4] stated: "There is no correlation with height or with the degree of stockiness or ranginess. Contrary, then, to the general impression, thick-set, stocky men are apparently no more likely to develop hypertension than are their tall, thin, asthenic-looking brethren."

Those who have contended that there is a correlation between body build and blood pressure have arrived at their conclusions through an impression of total weight rather than through one of the size of the skeletal frame, and generally without sufficient anthropometric and statistical support. Von Bernuth [5] observed: "The view held hitherto was simply supported by inspection and intuitive processes, which do

From the Department of Medicine, Northwestern University.

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The statistical and clerical work was done with the aid of the Work Projects Administration under the sponsorship of the Institute for Juvenile Research, Dr. Paul L. Schroeder, director.

1. Bauer, J.: Die konstitutionelle Disposition zu inneren Krankheiten, Berlin, Julius Springer, 1924.

2. Braun, L.: Constitution and the Circulatory System, Wien. klin. Wchnschr. **43**:142, 1930.

3. Hay, J.: The Significance of a Raised Blood Pressure, Brit. M. J. **2**:43, 1931.

4. Alvarez, W. C., and Stanley, L. L.: Blood Pressure in Six Thousand Prisoners and Four Hundred Prison Guards: Statistical Analysis, Arch. Int. Med. **46**:17 (July) 1930.

5. von Bernuth, F.: Constitution (Review of Literature), Monatschr. f. Kinderh. **71**:165 (Nov.) 1937.

not suffice. Exact measurements are necessary." Von Bernuth's observation is pointedly illustrated by the commonly accepted belief that flat-chested persons are more prone to tuberculosis—an opinion apparently the result of purely intuitive processes. Weisman's [6] recent monograph showed that the normal chest is flat and that the chest of the tuberculous patient is relatively deep.

A serious criticism of most of the existing studies on body build and blood pressure is that the series covered have been relatively small. Furthermore, in some studies the indexes of build that have been used do not adequately delineate types of build. In spite of this lack of rigidly controlled statistical studies, the prevailing opinion among medical writers is that there is a constitutional factor in the hypertensive diseases. [7]

Since there is no unanimity of opinion on the relation between gross body structure and blood pressure, any study clarifying this problem is of greatest importance. Backer [7a] stated:

> If a relationship between bodily habitus and blood pressure were now clearly established, both factors, the habitus as well as its corresponding arterial tension, would most likely have to be traced to a much deeper underlying *common cause* possibly appearing early in the course of ontogenetic events.

The morphologic structure is only one manifestation of the constitutional type of the person. The total constitution, that is, the constitution considered from the psychologic, immunologic, endocrinologic and other points of view, carries with it the susceptibilities to, and the potentialities of, disease. This paper deals only with the susceptibility to hypertension as associated with the gross body build aspect of constitution. Hurst [8] pointed out: "A better knowledge of constitution . . . should make it possible to prevent some diseases . . . [and] to recognize others in an earlier stage than is at present possible." The recognition of a relation of a type of body build to hypertension should make possible

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6. Weisman, S. A.: Your Chest Should Be Flat: The Deep Chest Makes Better Soil for Tuberculosis, Philadelphia, J. B. Lippincott Company, 1938.

7. (*a*) Backer, M.: Essential Hypertension: Constitutional Considerations, Am. J. M. Sc. **192**:395, 1936. (*b*) Palmer, R. S.: Etiologic Factors in Hypertension, New England J. Med. **205**:233, 1931. (*c*) Zipperlen, V. R.: Constitutional Investigations Among Hypertensives, Ztschr. f. Konstitutionslehre **16**:93, 1931. (*d*) Barach, J. H.: Constitutional Factors in Hypertensive Disease, J. A. M. A. **91**:1511 (Nov. 17) 1928. (*e*) Fishberg, A. M.: Hypertension and Nephritis, ed. 2, Philadelphia, Lea & Febiger, 1931. (*f*) Friedlander, A.: Hypotension, Medicine **6**:147, 1927. (*g*) Larimore, J. W.: A Study of Blood Pressure in Relation to Types of Bodily Habitus, Arch. Int. Med. **31**:567 (April) 1923.

8. Hurst, A. F.: The Constitiutional Factor in Disease, Brit. M. J. **1**:823, 1927.

the administration of preventive measures against this disease that now seems to be recognized as incurable. Hurst [8] further stated:

> It would seem obvious that in the practice of medicine the man is as worthy of study as the malady with which he is afflicted. But during the last twenty-five years the great advances in knowledge which have followed the application of bacteriological, biochemical, and physical methods to the investigation of disease have led to the comparative neglect of the constitutional factor. . . .

Before proceeding with this investigation of the relation of blood pressure to body build, it was necessary to find a simple method of grouping persons according to specific types of body build. The methods commonly used by anthropometrists and the European theorists on constitution were found to be, for the most part, too complex for practical clinical research. As Graves [9] has long pointed out, the necessary quantitative technics are merely means toward the discovering of qualitative differences. The goal is a constitutional theory that will aid clinical practice.

The first task in such a study of build as this would be to arrive at an index that would accurately delineate the two main types of body build, namely, (1) the thin, narrow-chested type, often designated as the long and thin one, and (2) the broad-chested, solid, stocky type. These opposing types merge into an intermediate one. Two extremes of build were recognized by the earliest medical writers. Hippocrates pointed out this gross division of the human race and established the two classes of build: habitus apoplecticus and habitus phthisicus. Gildea, Kahn and Mann [10] pointed out that "two large main groups stand out. These may be roughly denoted as the stocky in build at one pole as contrasted with the thin at the other." Similarly, Stockard [11] concluded: "The two groups into which almost all ordinary persons fall more or less exactly, may, therefore, be termed the *Linear Type* and the *Lateral Type*." It is a common practice among lay persons and professional men alike to designate the two obvious builds as either slender or broad. Terms like asthenic, hyposthenic, leptosomic, dolichomorphic, microsplanchnic and cerebral all refer to the linear type, while sthenic, hypersthenic, pyknic, brachymorphic, macrosplanchnic and digestive designate the broad, or lateral, type. For clinical practice, the importance of having a simple index for build, by means of which a quick estimate can be made of the person's gross type, cannot be overestimated.

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9. Graves, W. W.: Personal communication to the authors.

10. Gildea, E. F.; Kahn, E., and Mann, E. B.: The Relationship Between Body Build and Serum Lipoids and a Discussion of These Qualities as Pyknophilic and Leptophilic Factors in the Structure of the Personality, Am. J. Psychiat. **92**:1247, 1935.

11. Stockard, C. R.: Human Types and Growth Reactions, Am. J. Anat. **31**:261, 1923.

Such an index of build would have to take into account the person's height as well as his width. As Davenport [12] observed, a simple relation of breadth to height gives an excellent evaluation of a person's build. Most of the indexes used rely on these two basic measurements. The question of measuring the stature is a simple one, but the problem of arriving at the breadth introduces a few complications. To ascertain the breadth one might measure the intertrochanteric distance, or the intercristal width,[13] or the width, depth or circumference of the chest. The intertrochanteric or any hip measurement, however, introduces too large a sex variable. Moreover, it does not necessarily measure thoracic width or bulk. Davenport [12] stated:

> When I look at a man, or a photograph of one . . . and think "He is slender," it is because I make a mental comparison of his breadth (of shoulders or chest) with his height and find that his breadth in comparison with that of most men I know of that height is small; or if he is stout the diameter of the chest is large in relation to stature.

The thorax is, of course, the largest body surface or bulk that can be contrasted with height. Chest width and chest circumference stand out, then, as the two most desirable measures of breadth. Since Davenport [12] has pointed out that "chest circumference bears a nearly constant relation to chest diameter," it does not matter which of these measures is used. However, circumference is probably a slightly more accurate gage of total thoracic bulk, for diameter alone excludes the varying chest depth; circumference includes both width and depth.

In this study the circumference of the chest was divided by the height to produce a ratio similar to those of Brugsch,[14] Berliner [15] and Livi [16] and to the formula of the Marburg School [17] involving thoracic circum-

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12. Davenport, C. B.: Body-Build and Its Inheritance, Washington, D. C., Carnegie Institution of Washington, 1923.

13. Lucas, W. P., and Pryor, H. B.: Physical Measurements and Physiologic Processes in Young Children: Some Correlations, J. A. M. A. **97**:1127 (Oct. 17) 1931.

14. Brugsch, cited by Viola, G., and Benedetti, P.: Standardization of Anthropometric Measurements, Endoc. e pat. costit. **10**:446, 1935.

15. Berliner, M.: Height and Breadth Development, Ztschr. f. klin. Med. **108**:378, 1928.

16. Livi, cited by Graffi, E.: Body Proportions and Somatic Characteristics of a Group of Girl Students at the University of Bologna, Endoc. e pat. costit. **5**:392, 1930.

17. Data concerning this formula are cited by V. Wigert (Attempts at Anthropometric Determinations of Body Structure Types, Ztschr. f. d. ges. Neurol. u. Psychiat. **143**:651, 1933).

It has been pointed out by some authors that this chest/height index should be modified by squaring the height or using the square root of the chest. The only

ference and body length. This index can be determined from measurements quickly made in routine examinations and accurately delineates the classic types of build. At the same time the simplicity of the chest/height index makes it useful for statistical manipulation. Without rigidly controlled statistics on a large series one can hardly show a correlation between two variables like build and hypertension. Since this study aimed at a measure of skeletal configuration, it must be noted that the weight factor was ignored entirely. Nevertheless a variable amount of obesity was included in the measurement of the chest circumference.[18]

STATISTICAL ANALYSIS

To ascertain the correlation of body build and blood pressure, an unselected series of records containing the results of a complete physical examination conducted by the Life Extension Examiners in the Chicago office was analyzed. From each record an abstract was made of the height, weight, blood pressure, pulse rate and chest and girth measurements. The examination was well standardized, since the same six physicians made all of the examinations, and in many cases check-up readings among the various examiners were obtained. The chest measurement was taken with a steel tape just above the nipple line during quiet breathing; in the measuring of women the tape was placed higher to avoid the inclusion of excess mammary tissue. Height was

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rationale for this modification is that the chest is a two dimensional measurement whereas height is one dimensional. Actually, it makes no difference how these figures are manipulated, since the coefficients of correlation of systolic pressure to various modifications of the index remain practically unchanged. For example, the coefficients of correlation obtained for our subjects were as follows:

Correlation	1861 Men	1797 Women
C/H to systolic pressure	$= 0.184 \mp 0.022$	and 0.299 ∓ 0.022
C/H² to systolic pressure	$= 0.188 \mp 0.022$	and 0.266 ∓ 0.022
C/H³ to systolic pressure	$= 0.157 \mp 0.023$	and 0.235 ∓ 0.022
$\sqrt{C/H}$ to systolic pressure	$= 0.184 \mp 0.022$	and 0.280 ∓ 0.022
$\sqrt[3]{C/H}$ to systolic pressure	$= 0.153 \mp 0.023$	and 0.234 ∓ 0.022

With the formula $\sigma_D = \sqrt{\sigma_{\theta_1}^2 + \sigma_{\theta_2}^2 - 2r_{12}\,\sigma_{\theta_1}\,\sigma_{\theta_2}}$, the difference between any two of these coefficients would have to be at least 0.062 in order to be significant. Since the actual difference does not exceed 0.035 in any combination in the men and is only 0.065 between C/H and $\sqrt[3]{C/H}$ in the women, the modifications can add little to the value of the index. The C/H measure is used in this paper because it is the simplest and easiest to understand.

18. It is possible for a person of any build to be either underweight, medium weight or overweight; further, the person of linear or slender build, as well as the one of lateral build, may be either short or tall. These phases of the problem dealing with the interplay of obesity, height and build in their relations to hypertension have been dealt with in an article entitled "Hypertension, Obesity and Body Build" in the American Journal of Medical Science (**199**:819, 1940) and one entitled "Hypertension in Relation to Height: Its Variation with Body Build and Obesity" in a forthcoming issue of the Journal of Laboratory and Clinical Medicine.

measured on a specially designed apparatus in which the heels of the subject were placed against a backboard of a platform and the shoulders thrown back against a rod; the head was tilted and the subject asked to stretch to obtain the maximum height to $\frac{1}{10}$ inch (0.25 cm.). The group was composed of 3,658 persons: 1,861 were of the male and 1,797 of the female sex.

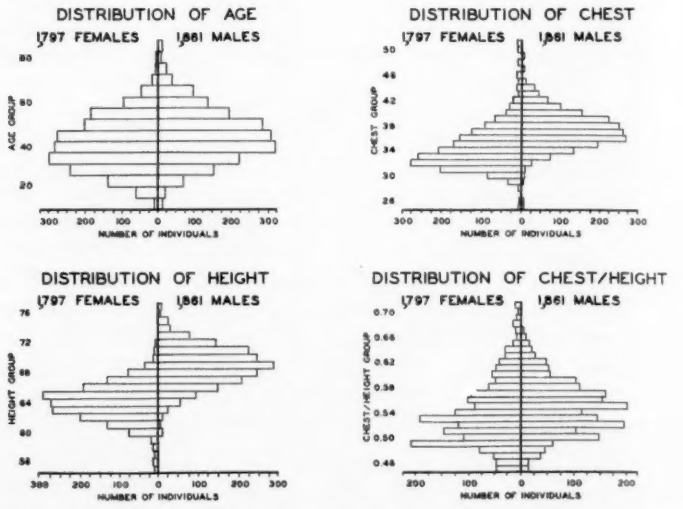

Fig. 1.—Charts illustrating the distribution of the physical measurements used in the study of body build and blood pressure. The statistical constants for these distributions are as follows:

	Age		Chest Circumference		Height		Chest/Height Ratio	
	Men	Women	Men	Women	Men	Women	Men	Women
Mean.....	43.0∓ 0.28	38.3∓ 0.27	37.0∓ 0.07	33.7∓ 0.07	68.3∓ 0.07	63.6∓ 0.06	0.543∓ 0.001	0.532∓ 0.001
Median.....	42.3	37.6	36.8	33.2	68.4	63.6	0.543	0.524
Mode.....	40.9	36.2	36.4	33.2	68.6	63.6	0.543	0.508
Standard deviation...	11.9	11.4	2.83	3.16	2.8	2.5	0.044	0.052
Standard range.....	31-55	27-50	34-40	30-36	65-71	61-66	0.50-0.59	0.48-0.58

Distribution of Ages.—Figure 1 shows that the ages of men were concentrated in the standard range[19] of 31 to 55 years. The ages of the women were concentrated between 27 to 50 years. The subjects were, therefore, essentially a middle-aged group at that period when clinical hypertension is most likely to make its early appearance.

19. A standard range is defined here as the range of one standard deviation on either side of the mean, roughly rounded out to the nearest whole number. For all practical purposes, if the curve is only moderately skew, this range includes a little more than two thirds of the group.

Distribution of Circumferences of Chest.—The chest circumferences of the men ranged from 24 to 47 inches (60.96 to 119.38 cm.) with a concentration in a standard range of about 34 to 40 inches (86.36 to 101.60 cm.). There was a slight increase in chest circumference up to about 40 years of age. The younger men (ages 20 to 30) had a chest circumference of about 34 inches (86.36 cm.). At 40 years and later the most usual chest measurement was 37 inches (93.98 cm.). The chest circumferences of the women ranged from 23 to 50 inches (58.42 to 127 cm.), with a standard range of from 30 to 36 inches (76.20 to 91.44 cm.). As with the male group, there was a slight increase with age in the chest circumference of the women.

Distribution According to Height.—The average height of the men was 68 3/10 inches (173.48 cm.), with a standard range of 65 to 71 inches (165.10 to 180.34 cm.). This average is only a few tenths of an inch lower than that observed in most other studies on the distribution of height.[20] The average height of the women was 63 6/10 inches (161.54 cm.), with a standard range of from 61 to 66 inches (154.94 to 167.64 cm.).

Distribution of Systolic Blood Pressures.—The distribution of systolic pressures is shown in table 1 to follow closely that of our larger series of 15,000 persons.[21] The average systolic pressure for the male group was 120 mm., though the mode was lower at 110 mm. The standard range showed that for the most part the pressures of the men ranged from 102 to 139 mm. Those for the female groups averaged 116 mm., with a mode of 112 mm. The standard range of pressure among the women was from 96 to 136 mm. Low pressures occurred more frequently among the women and higher pressures slightly less frequently. However, it is important to remember that the female group was a younger group than the male group and that young women have lower pressures than do young men, while older women show pressures slightly higher than those of older men.

Distribution of Diastolic Blood Pressures.—The diastolic pressures (table 1) for the men averaged 74.4 mm., with a modal pressure of 71.1

20. (*a*) Jackson, C. M.: The Physique of Male Students at the University of Minnesota: A Study in Constitutional Anatomy and Physiology, Am. J. Anat. **40**:59, 1927. (*b*) Jackson, C. M.: Physical Measurements of the Female Students at the University of Minnesota, with Special Reference to Body Build and Vital Capacity, Am. J. Phys. Anthropol. **12**:363, 1929. (*c*) Medico-Actuarial Investigation: Statistics of Height and Weight of Insured Persons, New York, Association of Life Insurance Medical Directors and the Actuarial Society of America, 1912. (*d*) Ireland, M. W.: The Medical Department of the United States Army in the World War, Washington, Government Printing Office, 1921, vol. 15, pt. 1.

21. Robinson, S. C., and Brucer, M. H.: The Range of Normal Blood Pressure, Arch. Int. Med. **64**:409 (Sept.) 1939.

TABLE 1.—*Relation of Chest/Height Ratio To Blood Pressures*

		Linear Build with Chest/Height Ratios of		Intermediate Build with Chest/Height Ratios of			Lateral Build with Chest/Height Ratios of		Chest/Height Ratios of All Types	Correlation Data		
		0.47 and Under	0.48 to 0.49	0.50 to 0.52	0.53 to 0.55	0.56 to 0.58	0.59 to 0.61	0.62 and Over			Chest/Height	Blood Pressure
Systolic pressure 1,861 men	Under 110 mm.	45	74	127	112	77	26	10	471			
	110 to 120 mm.	40	54	147	150	117	39	19	566			
	120 to 140 mm.	23	63	149	157	123	76	37	628	Mean	0.532∓0.001	119.9∓0.41
	140 mm. and over	5	7	30	51	57	23	23	196	Standard deviation	0.052	17.83
	Number of subjects	113	198	453	470	374	164	89	1,861	Skewness	0.462	0.56
										Coefficient variation	9.77	14.87
	Mean pressure	114	115	117	120	123	123	130	120	Coefficient correction	$r=0.184\mp0.022$	
	Median pressure	113	113	115	117	119	122	126	117	Correction ratio	$\eta=0.253$	
	Modal pressure	110	110	112	111	116	119	118	110	Test lin.	$\zeta=0.030\mp0.008$	
	Percentage under 110 mm.	40	37	28	24	21	16	11	25			
	Percentage 140 mm. and over	4	4	7	11	15	14	26	10			
Systolic pressure 1,797 women	Under 110 mm.	122	174	206	120	67	29	34	752			
	110 to 120 mm.	70	84	121	82	50	38	19	464			
	120 to 140 mm.	28	60	101	82	65	41	34	411	Mean	0.543∓0.001	116.0∓0.48
	140 mm. and over	5	8	29	33	26	36	33	170	Standard deviation	0.044	20.35
	Number of subjects	225	326	457	317	208	144	120	1,797	Skewness	.....	0.19
										Coefficient variation	8.10	17.54
	Mean pressure	109	110	114	115	120	128	129	116	Coefficient correction	$r=0.299\mp0.22$	
	Median pressure	109	109	111	114	116	120	123	112	Correction ratio	$\eta=0.309$	
	Modal pressure	108	105	107	113	112	115	110	112	Test lin.	$\zeta=0.006\mp0.003$	
	Percentage under 110 mm.	54	53	45	38	32	20	28	42			
	Percentage 140 mm. and over	2	3	6	10	13	25	28	10			
Diastolic pressure 1,861 men	Under 70 mm.	55	77	163	135	78	31	14	553			
	70 to 79 mm.	45	86	198	192	162	56	33	772			
	80 to 89 mm.	10	33	66	111	99	60	26	405	Mean	0.543∓0.001	74.4∓0.24
	90 mm. and over	3	2	26	32	35	17	16	131	Standard deviation	0.044	10.44
	Number of subjects	113	198	453	470	374	164	89	1,861	Skewness	.....	0.32
										Coefficient variation	8.10	14.3
	Mean pressure	71	71	73	75	77	77	79	74	Coefficient correction	$r=0.249\mp0.022$	
	Median pressure	70	72	72	73	75	79	79	73	Correction ratio	$\eta=0.263$	
	Modal pressure	70	73	71	71	71	82	77	71	Test lin.	$\zeta=0.007\mp0.004$	
	Percentage under 70 mm.	49	39	36	29	21	19	16	30			
	Percentage 90 mm. and over.	3	1	6	7	9	10	18	7			
Diastolic pressure 1,797 women	Under 70 mm.	135	203	239	138	72	41	43	871			
	70 to 79 mm.	69	96	157	106	72	46	25	571			
	80 to 89 mm.	16	23	38	52	46	36	31	242	Mean	0.532∓0.001	70.4∓0.28
	90 mm. and over	5	4	23	21	18	21	21	113	Standard deviation	0.052	11.66
	Number of subjects	225	326	457	317	208	144	120	1,797	Skewness	0.462	0.03
										Coefficient variation	9.77	16.56
	Mean pressure	67	67	69	71	74	76	77	70	Coefficient correction	$r=0.279\mp0.002$	
	Median pressure	65	66	69	71	73	75	76	70	Correction ratio	$\eta=0.312$	
	Modal pressure	61	64	69	71	72	71	74	70	Test lin.	$\zeta=0.019\mp0.006$	
	Percentage under 70 mm.	69	62	52	44	35	29	36	49			
	Percentage 90 mm. and over.	2	1	5	7	9	15	18	6			

mm. The standard range was from 64 to 85 mm. As in the case of systolic pressure, the average diastolic pressure for the women was lower, 70.4 mm., with a mode of 70.1 mm. The standard range was from 59 to 82 mm. The female group showed a greater frequency of low pressures and a smaller one of high pressures than did the male group. This difference is due to the high incidence of the lower pressures among younger women. At the older ages the distribution of diastolic pressures among the female group was similar to that among the male group.

Distribution of the Chest/Height Ratio.—The index obtained by dividing the chest circumference by the height was used in this study to differentiate the broad type of build from the narrow one. The simplicity of this index is its main asset. Further, it is to be noted that the measure of weight is not used at all to arrive at this index. Roughly, the index can be sketched easily by the rule-of-thumb statement that the chest circumference should be one-half the height, in other words, that the chest/height ratio should be 0.50. For the purpose of comparing type characteristics, three classes of persons were established on the basis of the following types of build: (1) a linear type, with a chest/height ratio of less than 0.50 (chest measurement less than one-half the height); (2) an intermediate type of build, with a ratio within the standard range of 0.50 to 0.59, and (3) a lateral type, with an index of 0.59 or over (chest circumference very large in relation to height). This is a purely arbitrary division and is used only for the purpose of comparing extremes. Throughout this study finer subdivisions in type of build are usually given which merge from one type into the other.

The mode of the chest/height distribution was 0.54 for the men with a standard range of from 0.50 to 0.59. As would be expected, the women showed a narrower type of build. The average chest/height ratio for women was 0.53 with a mode slightly less than 0.51; a standard deviation of 0.05 gave a standard range for women of 0.48 to 0.58. The distribution curve of the build of women, however, was more platykurtic, and the greater frequency of very narrow types depressed the measures of central tendency. Seventeen per cent of men and 31 per cent of women had a chest circumference less than one-half their height (linear or slender build, under 0.50), and 12 per cent of both men and women had chests much larger than one-half their height (lateral or broad build, over 0.59). Actually there are as many extremely broad builds among women as among men.

Changes in Chest Circumference and Body Build with Age.—The men showed a gradual increase in chest circumference up to 50 years of age. At 20 years the average chest circumference was 34 to 35 inches

(86.36 to 88.9 cm.). This average increased to 37 or 38 inches (91.44 or 96.52 cm.) at the end of the fourth decade and remained at 37 inches with only a slight tendency to decrease in the very old men. None of the extremely large chests occurred in the very old age groups. This fact suggests for the men with large chests a high death rate in the previous decades. The women showed a similar rise from 32 inches (81.28 cm.) at the age 20 to 35 inches at the end of the fifth decade, after which there was a tendency toward decrease in chest circumference.[22]

The chest/height ratio also showed the tendency observed in the case of chest circumference[23] (table 2). The ratio of the men showed a definite tendency to rise from an average of 0.51 (the height roughly twice the chest circumference) at 20 years to 0.55 at age of 40 years. The slight rise after this age was probably due to additional deposition of fat over the chest. Among the women the chest/height ratio was similarly increased with age. The increase was gradual up to the age

TABLE 2.—*Ratio of the Mean Chest/Height Ratio at Various Ages*

Age Groups	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 to 64	65 to 69	70 and Over	All Ages
1,861 men.....	0.486	0.512	0.524	0.531	0.540	0.550	0.553	0.556	0.559	0.551	0.546	0.560	0.543
1,797 women.....	0.501	0.504	0.507	0.516	0.532	0.545	0.563	0.561	0.553	0.558	0.554	0.519	0.532

of 35, after which it became more rapid. This rapid rise in middle age was probably due to the influence of deposition of fat. As will be shown in another study,[18] this disposition is in itself related to build and does not appreciably affect the division of the linear and the lateral type by the chest/height ratio. Except in a few abnormally obese persons, the deposition of fat over the chest does not change the index by more than 0.02 unit.

22. The following coefficients of correlation of age with chest circumference were obtained:

Men	Women
$r = 0.216 \mp 0.022$	$r = 0.360 \mp 0.021$
$\eta = 0.324$	$\eta = 0.408$
$\zeta = 0.058 \mp 0.011$	$\zeta = 0.036 \mp 0.009$

Thus, the correlations were fairly good, though decidedly nonlinear. There was definitely a growth in the chest circumference during the third decade of life.

23. The following coefficients of correlation of age to chest/height ratio were obtained:

Men	Women
$r = 0.244 \mp 0.022$	$r = 0.400 \mp 0.020$
$\eta = 0.318$	$\eta = 0.430$
$\zeta = 0.041 \mp 0.009$	$\zeta = 0.025 \mp 0.007$

As was true with chest circumference, the correlation was nonlinear, though in the case of chest/height ratio the correlation was more linear than in that of chest circumference. The correlation for the women was far more significant and more linear. This again was probably due to the steadier accumulation of fat on the chest after age of 35 years, when the curve for men tends to level off.

Relation of Build to Blood Pressure.—There is a significant statistical relation between body build and systolic pressure. In the group of 1,861 men there was a steady rise in mean systolic pressure as the build progressed toward the lateral extreme (table 1). Those with very linear builds (chest/height ratio of 0.47 and under) showed an average pressure of 114 mm. This average rose to 120 mm. in the group with intermediate builds and rose further to 130 mm. in the group having very lateral builds. That this is not an artefact produced by a small number of hypertensive persons of lateral build is shown by the fact that the median and modal pressures followed the same tendency, and both rose from 110 mm. in persons of linear build to over 118 mm. in those of lateral build.

Diastolic pressure shows the same relation to build as does systolic pressure (table 1). With a progression toward the lateral extreme there was an increase in both the mean and the modal pressure. The mean diastolic pressure for the men of very linear build was around 70 mm., whereas those of the lateral type showed an average diastolic pressure of around 79 mm. The median and modal diastolic pressures rose from 70 mm. in the men of linear build to over 77 mm. in those of lateral or broad build.

The group of 1,797 women showed a similar tendency. Those of the linear type of build had systolic pressures under 110 mm. on the average, while those of the lateral type showed an average systolic pressure of almost 130 mm. The mean, median and modal systolic pressures all showed the same tendency to rise as the frame widened.[24]

The female group showed a similar difference in diastolic pressure between persons of narrow and those of broad builds. The women of very linear build averaged a diastolic pressure of less than 67 mm., slightly lower than that of the men of linear build, while the women of lateral build averaged a diastolic pressure of around 77 mm. The

24. The correlations between chest/height ratio and systolic pressure were significant and positive (table 1). That for the male group was only insignificantly nonlinear, while that for the female group was definitely linear. The greater significance of the correlation for the female group may be explained on the basis of the previously noted accumulation of fat. For the female group the correlation of chest/height to weight was 0.70, which is 0.09 greater than the corresponding correlation for the male group. These observations indicate that the females of lateral build are subjected to the hazard of obesity to a greater extent than are the males. This is borne out by the fact that with weight held constant the partial correlations of chest/height to systolic pressure show a significant difference. The partial correlations observed in this study were as follows:

Men: $r_{cs.w} = 0.100$ Women: $r_{cs.w} = 0.199$

median and modal diastolic pressures exhibited the same tendency to rise as the build broadened toward the lateral extreme.[25]

Distribution of Low and High Pressures in Build Groups.—A comparison of the distributions of the low and high pressures among the persons of linear as contrasted with those of lateral build is more revealing. Only 4 per cent of the male group with linear build had systolic pressures over 140 mm., while 22 per cent with lateral build were definitely hypertensive (fig. 2). Similarly, only 2 per cent of the women with linear, or thin, build had systolic pressures over 140 mm., while 27 per cent of the women with lateral, or broad, build were hyper-

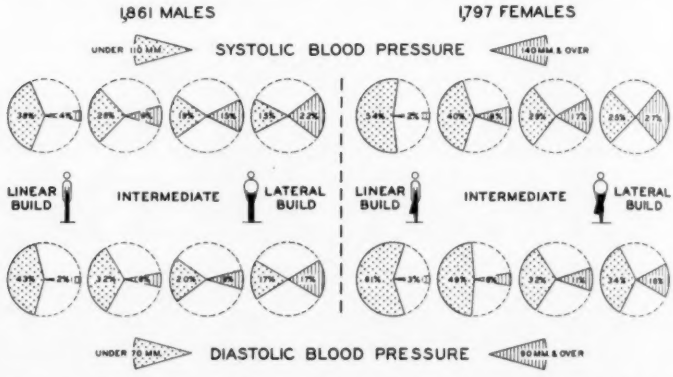

Fig. 2.—Comparative distribution of low and high pressures in various body build groups. Viewed in the direction from the linear to the lateral build, the cross-hatched sections show the increase in the incidence of hypertension, whereas the dotted sections show the decrease in the incidence of low pressure. This holds true for both the male and the female sex and for diastolic as well as systolic pressure. (Chart prepared by W. P. A.)

25. The correlations between chest/height ratio and diastolic pressure show a significant relation (table 1). At first glance it might seem that the male-female reversal of linearity relations is a contradiction of the explanation given in footnote 24 concerning the systolic correlation. However, in the first place the tendency for diastolic pressure to correlate with the chest/height ratio is the same, though not as marked; secondly, the correlation for neither the male nor the female group is significantly nonlinear. The explanation for the small degree of difference between correlations for men and women given in footnote 24 would be correct for the difference in the diastolic correlation only if the correlation of diastolic pressure to weight for the female group was almost identical to that for the male group. Actually, for the female group the correlation of diastolic pressure to obesity is 0.22, identical with the corresponding correlation for the male group, while in the case of the correlation of systolic pressure to obesity that for the female group at 0.18 is only 0.02 greater than that for the male. This fact also explains the greater (though not significant) test for linearity in the diastolic correlation for the female group.

tensive. The relation was reversed in respect to the low pressures. Among the persons of linear build, 38 per cent of the men and 54 per cent of the women had systolic pressures under 110 mm., while among those of lateral build only 15 per cent of the men and 25 per cent of the women had the same low systolic pressures.

The comparison of the distributions of low and high diastolic pressures gives results similar to those involving the systolic pressures. In figure 2 it is seen that whereas only 2 per cent of the persons of linear build had high diastolic pressures, 17 per cent of those of lateral build had diastolic pressures over 90 mm. This contrast speaks for an unusual difference in susceptibility to hypertension among persons of the contrasting extremes of body build. Conversely, 43 per cent of the men of linear build and only 17 per cent of those of lateral build had low diastolic pressures, while 60 per cent of the women of linear build and only 34 per cent of those of lateral build had diastolic pressures under 70 mm. Thus it is apparent that the low pressures are predominantly found in persons of linear build and the high pressures in those of lateral build. Just as important as this association is the fact that the person of the linear type of build tends to repel high pressure and the one of the lateral type tends to repel low pressure.

Thus far the differences in the incidence of high and low pressures within specific body build groups have been observed. This was done by holding the build constant and making the pressure the dependent variable. If the correlation actually holds true, there should be a similar difference in the incidence of linear and lateral builds within the specific blood pressure groups. Data obtained with blood pressure held constant and with build as the dependent variable will now be presented.

That this association is applicable in either direction is illustrated in figure 3, in which the groupings are reversed. Of the persons with low systolic pressure, 28 per cent of the men were of linear build while only 8 per cent were of lateral build; similarly, 40 per cent of the women were of linear build while only 8 per cent were of lateral build. Conversely, of the hypertensive men, only 6 per cent were of the linear type while fully 24 per cent were of the lateral type; and of the hypertensive women, 8 per cent were of the linear type while 41 per cent were of the lateral type.

In the case of diastolic pressure the relations are similar. Of the persons with low diastolic pressure (under 70 mm.), there was in the male group a great difference in representation of the two extreme types of build, for 26 per cent were of linear build and only 7 per cent were of lateral build. In the female group 39 per cent were of linear build and 9 per cent of lateral build. Conversely, of the persons with high diastolic pressure (over 90 mm.), 25 per cent of the men were of the

lateral type while only 3 per cent were of the linear type, and 37 per cent of the women were of the lateral type while only 8 per cent were of the linear type. The data indicate, therefore, that in any group with low pressures the incidence of linear builds is far greater than that of lateral builds, and that in any group with high pressures the incidence of lateral builds is far greater than that of linear builds.

The ratio of actual to expected incidence [26] demonstrates in another way the same tendency for low pressure to be associated with linear build and high pressure with lateral build. The ratio was calculated

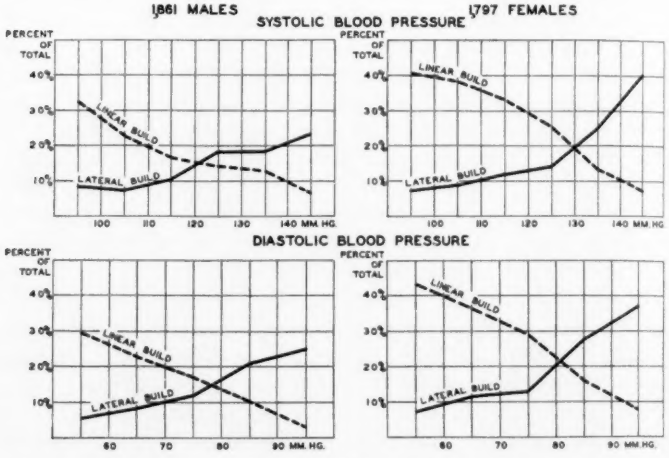

Fig. 3.—Comparative distribution of build at various levels of blood pressure. Linear build is most common in the low pressure groups, in which lateral build is comparatively rare. Lateral build is most common in the high pressure groups, in which linear build is comparatively rare. (Chart prepared by W. P. A.)

26. The ratio of per cent actual to expected incidence is simply calculated and is of use in illustrating the relative effect of the extremes of one array on the dispersion of another correlated array. The technic is used here to show the unusual influence of a broad build on blood pressure. For example, if, in any random group of 100 men, 22 are of the linear type of build and 13 are of the lateral type, and if there is no correlation of build to blood pressure, then the same ratio of 22 linear to 13 lateral should hold true in any group of persons whether they have low, medium or high pressures. This, however, is not the case. Among a group of 100 hypertensive persons, there are actually only 9 of the linear type as compared to 23 of the lateral type. This gives a ratio of actual to expected incidence of 9:22, or only 41 per cent of the expected incidence of linear build among hypertensive persons, as compared with the ratio of 23:13, or 177 per cent of expected incidence of lateral build among hypertensive persons. Simply stated, this means that among hypertensive men lateral build predominates in a ratio of over 4:1.

separately for each body build–pressure group so as to illustrate the comparative differences in the expectancy of high and low pressure and to standardize the variations in the incidence according to types of build. Since there were 22 per cent linear builds to only 13 per cent lateral builds, the ratio of actual to expected ratio corrects for this uneven distribution. The ratio was consistent with differences in the blood pressure that were observed in comparisons of the measures of central tendency of distribution and in the comparisons of incidence within specific body build–pressure groups.

A comparison of the ratios of actual to expected incidence was first made for the groups having extreme build (table 3). The men of lateral build, or the broad-chested type, had more than four times the expectancy of systolic hypertension that the men of linear build, or the

TABLE 3.—*Ratio of Actual to Expected Incidence of Body Build (Measured By Chest/Height) According to Systolic Pressure* *

Type of Build	1,861 Men Blood Pressure			1,797 Women Blood Pressure		
	Low	Moderate	High	Low	Moderate	High
Linear	148	87	39	128	90	26
Intermediate	91	105	106	89	106	104
Lateral	62	108	177	57	107	293

*For this and subsequent tables, the following classifications are used: low systolic pressure, under 110 mm.; moderate systolic pressure, 110 to 139 mm.; high systolic pressure, 140 mm. and over; low diastolic pressure, under 70 mm.; moderate diastolic pressure, 70 to 89 mm.; high systolic pressure, 90 mm. and over; linear body build, chest/height ratio under 0.51; intermediate body build, chest/height ratio of 0.51 to 0.58; lateral body build, chest/height ratio of 0.59 and over.

In comparing the observed distributions, chi square was below the 0.0001 per cent level of significance.

narrow-chested type had, and less than one-half the expectancy of low pressure. The difference was even more striking among the women. The women of lateral, or broad, build had an almost eleven times greater expectancy of high systolic pressure than the women of linear build and less than one half the expectancy of low pressure.

Another illustrative comparison is of the ratios of actual to expected incidence made between groups with extreme pressure within each group representing types of body build. In any random series of 100 men of lateral build there should be 3 with systolic hypertension to every 1 person with low pressure. A group of women of lateral builds would show an even more striking difference: 5 would be hypertensive to every 1 who had low pressure. The situation is reversed in the groups with linear, or narrow-chested build: The men of linear build would have 5 persons with low systolic pressure for every 2 with high pressure. The women of linear build would have 5 persons with low systolic pressure to every one with high systolic pressure.

In the case of diastolic pressure the ratio shows similar tendencies (table 4). Comparison first of the groups having the extreme types of build shows the men of the lateral, or the broad, type to have more than seven times the expectancy of diastolic hypertension than the men

TABLE 4.—*Ratio of Actual to Expected Incidence of Body Build (Measured By Chest/Height) According to Diastolic Pressure* *

Type of Build	1,861 Men Blood Pressure			1,797 Women Blood Pressure		
	Low	Moderate	High	Low	Moderate	High
Linear	148	83	26	123	82	33
Intermediate	91	103	108	89	109	106
Lateral	62	115	192	71	121	264

* Same footnote as for table 3.

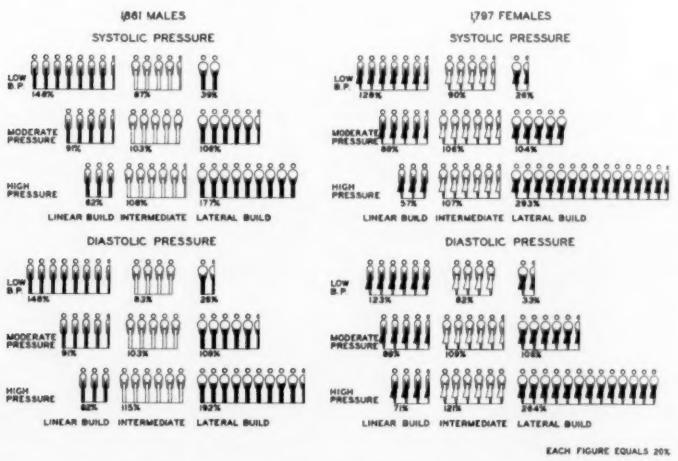

Fig. 4.—Influence of body build on blood pressure, showing the per cent ratio of actual to the expected incidence (see text), which illustrates the comparative association of low and high pressures with linear and with lateral build. Linear build has the greatest representation in the group with low pressure and the smallest representation in the group with high pressure. Conversely, lateral build has the greatest representation in the group with high pressure and the smallest representation in the group with low pressure. (Chart prepared by W. P. A.)

of linear build and less than one-half the expectancy of low diastolic pressure. The women of lateral build are shown to have eight times the expectancy of diastolic hypertension that women of linear build have and only slightly more than one-half the expectancy of low pressure.

A second comparison of the ratio of actual to expected incidence for the groups with extreme pressures within each build group shows that in

any random group of men of lateral build there would be 3 with high diastolic pressures to every 1 with low pressure (table 4). In a random group of women with lateral pressure there would be 7 with high diastolic pressures to every 2 with low diastolic pressures. In the groups with linear or slender build the situation is reversed. A group of men of linear build would include 6 with low diastolic pressure to every 1 with high diastolic pressure, and a group of women of linear build would have 3 persons with low pressure to every one with high pressure (fig. 4).

It is apparent from this evidence that as the group progresses toward the lateral, or broad-chested, build the chances of hypertension developing become progressively greater, and the chances of a low pressure developing become progressively smaller.

TABLE 5.—*Mean Systolic Pressure of Persons of Various Builds in Each Age Group*

		Age Groups								
Subjects Studied	Type of Build	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 and Over
1,861 men.....	Linear	118	117	111	113	114	110	113	119	128
	Intermediate	120	118	116	116	118	121	124	125	132
	Lateral	120	120	122	120	121	127	124	138	136
1,797 women.....	Linear	107	105	109	111	114	112	119	125	138
	Intermediate	106	108	111	113	117	123	121	134	142
	Lateral	123	113	116	120	124	130	125	155	155

Age as a Factor in the Relation of Body Build to Blood Pressure.—The age factor has not yet been taken into consideration. Table 5 shows that the tendencies which have already been pointed out roughly hold true at every age. Among our subjects, at every age the persons of broad build showed a higher pressure than the persons of narrow build. This should not be surprising. In a previous paper it was reported that the hypertensive pressures in older persons almost invariably occur among those who in youth had slightly elevated pressures. Hence, though the difference might not be so great in young men as in older ones, it should be apparent. As concerns systolic pressure the men of linear build as well as those of intermediate build showed a slightly decreased pressure during the fourth decade. This phenomenon has been noticed in most of the studies on the systolic blood pressure of young men.[27] Aside from this change, the men with linear build did not show an increased systolic pressure until late in life. Those with the lateral type of build began adult life with a higher systolic pressure and an

27. (*a*) Alvarez, W. C.; Wulzen, R., and Mahoney, L. J.: Blood Pressures in Fifteen Thousand University Freshmen, Arch. Int. Med. **32**:17 (July) 1923. (*b*) Johnson, W. M.: Tobacco Smoking: Clinical Study, J. A. M. A. **93**:655 (Aug. 31) 1929.

early increase to very high levels. The women of linear build did not show an appreciable increase in systolic pressure until after the age of 50 years. The women of the lateral type were already registering average pressures of over 120 mm. when they were 40 years of age. In every age group the women of lateral build showed a higher mean systolic pressure.

TABLE 6.—*Mean Diastolic Pressure of Persons of Various Builds in Each Age Group*

		Age Groups							
Subjects Studied	Type of Build	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 and Over
1,861 men	Linear	71	71	70	72	73	71	72	74	72
	Intermediate	73	70	72	73	75	76	77	77	77
	Lateral	75	80	77	77	79	78	77	83	77*
1,797 women	Linear	64	64	67	68	70	70	75	75	75
	Intermediate	64	66	68	70	72	75	74	77	81
	Lateral	73	70	73	74	76	77	75	88	83

* Insufficient distribution—less than 15 persons.

TABLE 7.—*Incidence of Low and High Systolic Pressures in Persons of Linear and Lateral Builds in Various Age Groups*

		Age Groups and Body Build									
		20 to 29		30 to 39		40 to 49		50 to 59		60 and Over	
		Linear	Lateral	Linear	Lateral	Linear	Lateral	Linear	Lateral	Linear	Lateral
1,861 men	Percentage incidence of low pressures (under 110 mm.)	28	17	45	15	45	18	40	14	17	3
	Percentage incidence of high pressures (140 mm. and over)	4	8*	3	8	3	16	4	22	17	39
1,797 women	Percentage incidence of low pressures (under 110 mm.)	65	18	51	34	42	24	35	20	17*	7
	Percentage incidence of high pressures (140 mm. and over)	0	0	1	16	5	24	14	40	50*	57

* Insufficient distribution—less than 15 persons. In comparing the observed frequencies in linear and lateral build, chi square is below the 1 per cent level of significance; this is true for each age group.

In the case of diastolic pressure the age factor shows similar tendencies (table 6). The mean diastolic pressure, except in two erratic groups, was consistently higher in the men and women of lateral or broad, type than in those of the linear, or slender, type. The men of linear build maintained about the same pressure throughout life, while the men of lateral build tended to show an increasing pressure. The

women of both types showed an increase in mean pressure, but those of lateral build showed an increase to a greater extent and on a higher level.

The incidence of low and of high systolic pressure in the various age groups is more illustrative of the differences in distribution (table 7). The incidence of low systolic pressure was very high among persons of linear build in all age groups as compared with a low incidence among the persons with lateral build.

This difference was least marked in men before 30 years and very striking until the age of 60, after which it became very marked. In the women it was most marked under 30 years and decreased somewhat

TABLE 8.—*Incidence of Low and High Diastolic Pressures Among Persons of Linear and Lateral Builds in Various Age Groups*

		Age Groups and Body Build									
		20 to 29		30 to 39		40 to 49		50 to 59		60 and Over	
		Linear	Lateral	Linear	Lateral	Linear	Lateral	Linear	Lateral	Linear	Lateral
1,861 men	Percentage incidence of low pressures (under 80 mm.)	43	8*	40	23	42	19	32	16	44	15
	Percentage incidence of high pressures (90 mm. and over)	1	0*	0	6	2	17	0	16	11	12
1,797 women	Percentage incidence of low pressures (under 70 mm.)	70	36	61	43	46	33	31	22	33*	7
	Percentage incidence of high pressures (90 mm. and over)	0	0	1	11	4	16	10	22	17*	29

* Insufficient distribution—less than 15 persons. In comparing the observed frequencies in linear and lateral build, chi square is below the 1 per cent level of significance; this is true for each age group.

later in life. This is probably due to the very strong tendency for young women to have low pressures regardless of their build. Conversely, the incidence of high systolic pressure was lowest among the persons of linear build (only after the sixtieth year does it rise in men), while the incidence of high systolic pressure among the men and women of lateral build steadily increased with each decade.

The incidence relations in diastolic pressures (table 8) show much the same tendencies as were observed in systolic pressure. In every age group studied low pressure predominated among the men and women of linear build and high pressure predominated among those of lateral build. The incidence of high diastolic pressures in the men of linear build was constant until very late in life; in the women it slowly rose but became significant only after the age of 50. The incidence of low pressures was nearly constant in the men of linear build throughout life. It is well known that any group of women will have a greater

incidence of the lower pressures than men in the younger age groups; this is especially true of slender women. Consequently, the decreases with advancing age in the incidence of low pressures in women of linear build is to be expected. Among the broad-chested men and women the incidence of low pressure decreased after the age of 30, while the incidence of high pressures increased.

COMMENT

In order to determine what relation exists between a person's build and his blood pressure, we have statistically analyzed the periodic health examination records of 3,658 persons. A simple ratio of width to height, calculated in terms of chest circumference divided by the standing height, was used. With this index the persons were divided into groups of (1) a linear, or slender, type of build, consisting of those with very narrow chests; (2) of a lateral type of build, those with very broad chests, and (3) of an intermediate type of build. This distinction of the persons of extremely broad build from those of extremely narrow build is obvious even to clinicians who have never formally applied anthropometric technics. It must be remembered that in making gross morphologic divisions, such as linear and lateral, only the beginnings of anthropometry are involved. To be sure, hypertension will appear in persons of both types, but for every person of narrow build having hypertension there will be 7 persons of broad build. For each of the persons of linear, or slender, build having a high pressure there will be 10 persons of linear build having pressures under 110 mm. It is true that among a group with broad lateral builds some will have low pressure. This does not vitiate the relation of hypertension and lateral build, because for every person of lateral build with low pressure there will be 4 of lateral build with high pressures.

That there is a correlation between body build and blood pressure should not be surprising. The clinical impression of the hypertensive persons has always been of a large, broad-chested person. However, this impression has always been confused with that of obesity. From a study already published,[28] it is apparent that observations made with measurements of weight held constant show the association of hypertension with lateral build to be even more striking than the well known association of hypertension with obesity.[28] It would seem from the

28. The partial correlation of chest/height to systolic blood pressure with weight held constant is $r_{ce.w} = 0.100$; the partial correlation of weight to systolic blood pressure with chest/height held constant is $r_{ce.w} = 0.077$. In other words, the more significant correlation is between chest/height and systolic blood pressure. A complete analysis of the obesity-hypertension relation is presented in an article, "Obesity and Hypertension" by S. C. Robinson, M. Brucer and I. Mass (J. Lab. & Clin. Med. **25**:807, 1940).

additional fact that obesity itself has a strong association with build, that the obesity-hypertension relation is really to a great extent a build-hypertension relation.

With the morphologic habitus thus definitely proved to be a part of the syndrome of hypertension, the first and most obvious implication is that hypertension must be a hereditary phenomenon. Baldwin's [29] work with the growth characteristics of children and Davenport's [12] work with inheritance and build firmly established the widely known fact that the structure of the body is an inherited characteristic. Since in this paper hypertension has been shown to be correlated to the lateral, or broad, build and low pressure to the linear, or thin, build, the hereditary predisposition to normal pressure and hypertension must be considered an established fact.

If heredity is the main determinant of body build and if human constitution in turn is correlated to hypertension, it would be interesting to contemplate which build more truly represents the human biologic and evolutionary pattern. In other words, what is the normal build? Purely statistical reasoning on contemporary series would choose the modal, or intermediate type. If this is correct, then both the lateral and the linear build group should be looked on as equally deviant from the true normal. On the other hand, Gildea, Kahn and Mann [10] and others have expressed the opinion that the lateral build is more truly representative of the human race. In this case the person of linear, or thin, build is the deviant. This implies that man's original frame was of the lateral type, and studies of early man support this view. Reconstructions of the paleolithic man show him to have been short and stocky, emphasizing a kinship to our higher simian ancestors. The linear build would then represent evolutionary changes away from the broad pattern. Such considerations of the biologic place of the respective builds of man, especially as they relate to the evolutionary scale, may throw light on the classification of disease and possibly on its causes. The study of the trend of disease in the evolution and growth of the human species may lead to valuable contributions in the elucidation of the origins of hypertension. In this respect a study of the disease picture among primitive peoples would be helpful.

In any case, whichever build represents ascent or descent in the evolutionary scale, it is safe to say that from the standpoint of longevity, the linear build is more desirable. There is substantial statistical evidence that the person with lateral build does not reach old age as frequently as does the one with linear build. In our own data the mean, the median and the modal chest circumference reach a peak at about the sixth decade and then decrease. None of the extremely large chests

29. Baldwin, B. T.: The Physical Growth of Children from Birth to Maturity, Studies in Child Welfare, Iowa City, University of Iowa, 1921, vol. 1, no. 1.

are observed in the older age groups. A consideration of the diseases to which each build group is predisposed seems to lend support to this conception. Obesity, which is positively associated with an increased mortality, is a much greater hazard of the group with lateral build than of that with linear build.[30]

Practically all of the cardiovascular diseases, especially hypertension, and their accompanying high mortality, occur more frequently in persons of the obese and lateral types. It is therefore clear that the person of linear build will outlive the one of lateral build. On the other hand, while the person of lateral build dies early, it is contended by some writers that he lives a more efficient life. The diseases associated with lateral build are not the diseases that cripple the patient's efficiency during his most productive years. The impression has already gained headway that the person of the linear build and low pressure type "lives long but lives miserably." There is no proof for such a statement. More study of the diseases in each build group is necessary.

It would be well, not only from the standpoint of clinical research but also from that of practical medicine, to bring together for coordinated study data on the diseases that seem to occur predominantly in persons of select body build groups. For example, the lateral type of body build accompanied by obesity is intimately associated with diseases of the myocardium and the circulatory system.[31] with arteriosclerosis,[32] with diabetes [33] and with toxemia of pregnancy.[34] These few by no means exhaust the list. On the other hand, the person of linear build is most often underweight. He tends to be immune to the diseases associated with the lateral build. He is susceptible to gastroduodenal ulcer and dyspepsia,[35] to exophthalmic goiter and neurocirculatory asthenia,[36] to

30. The coefficient of correlation of chest/height ratio to weight was 0.612 ± 0.014 for the male group and 0.708 ± 0.014 for the female group.

31. Costanzo, A.: Costituzione e mortalitá, Societá e detrice vita e pensiero, Milan, 1936.

32. Arteriosclerosis in Vienna, Foreign Letters, J. A. M. A. **103**:1247 (Oct. 20) 1934.

33. (*a*) Joslin, E. P.: Treatment of Diabetes Meliitus, ed. 6, Philadelphia, Lea & Febiger, 1937. (*b*) Master, A. M., and Oppenheimer, E. L.: A Study of Obesity: Circulatory, Roentgen-Ray and Electrocardiographic Investigations, J. A. M. A. **92**:1652 (May 18) 1929. (*c*) Gottschick, J.: Constitutional Pathological Observations in a Family with Diabetic Members, Ztschr. f. menschl. Vererb.- u. Konstitutionslehre **19**:585, 1935.

34. Herrick, W. W., and Tillman, A. J. B.: The Mild Toxemias of Late Pregnancy (Their Relation to Cardiovascular and Renal Disease), Am. J. Obst. & Gynec. **31**:832, 1936.

35. Robinson, S. C.: Exophthalmic Goiter and Gastroduodenal Ulcer: Two Constitutionally Different Diseases with Note on Pernicious Anemia, Illinois M. J. **73**:210, 1938.

36. Crile, G.: Diseases Peculiar to Civilized Man, New York, The Macmillan Company, 1934.

migraine [37] and to some neuroses.[38] Rheumatism, anemia and various "general infections" have also been found to be characteristic anomalies of persons of linear build.[39] Visceroptosis has long been known to be a part of the asthenic picture.[40]

The constitutional habitus is not the only common factor determining the classification of these diseases. Emotional conflict is common to the group with linear build that has ulcer, goiter, asthenia and migraine. Even more basic physiologic properties are possibly correlated to build. Investigators have found differentiations in types of build on the basis of blood chemistry levels,[41] acid-base equilibrium and basal metabolism,[42] reactions to drugs,[43] color and form reaction,[44] and behavior patterns.[45] As Cohen [46] pointed out, "there seems to be an intimate relation between biochemical, anatomical and mental changes."

It is not to be inferred that the type of build as such causes disease. Not every patient with lateral build is hypertensive or even potentially hypertensive. It can be seen, however, that the various morphologic

37. Braun, E., and Schellong, F.: Concerning the Constitutional Bases of Essential Hypertension, Deutsche med. Wchnschr. **62**:371, 1936.

38. (*a*) Kretschmer, E.: Physique and Character, translated by W. J. H. Sprott, New York, Harcourt Brace and Company, Inc., 1926. (*b*) Brandt, W.: The Biological Differences Between Pyknics and Leptosomes, Deutsche med. Wchnschr. **62**:501, 1936.

39. (*a*) Edens, E.: Constitution as a Basis for Disease, Klin. Wchnschr. **17**: 433, 1938. (*b*) Davenport.[12]

40. (*a*) Osler, W.: The Principles and Practice of Medicine, ed. 13, revised by Henry A. Christian, New York, D. Appleton-Century Company, Inc., 1938. (*b*) Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1928, vol. 6. (*c*) Musser, J. H.: Internal Medicine, ed. 2, Philadelphia, Lea & Febiger, 1934. (*d*) Fossier, A. E.: Cause of Essential Hypotension, Am. J. M. Sc. **171**:496, 1926. (*e*) Backer.[7a] (*f*) Crile.[36]

41. (*a*) Carrière, G.; Huriez, C.; Leperre, and Sence: The Blood of Hypertensives, Arch. d. mal. du cœur **28**:549, 1935. (*b*) Kahler, H.: The Question of Hyperglycemia in Diseased Conditions with High Blood Pressure, Wien. Arch. f. inn. Med. **4**:129, 1922. (*c*) Kylin, E.: Hypertension and Diabetes Mellitus, Zentralbl. f. inn. Med. **42**:873, 1921. (*d*) Ogilvie, R. F.: Sugar Tolerance in Obese Subjects, Quart. J. Med. **28**:345, 1935.

42. (*a*) Borgard, W.: Constitution and Basal Metabolism, Ztschr. f. klin. Med. **121**:737, 1932. (*b*) Stockard.[11] (*c*) Means, J. H.: Studies of the Basal Metabolism in Obesity and Pituitary Disease, J. M. Research **32**:121, 1915.

43. Hertz, T.: Pharmacodynamic Investigations on Constitutional Types, Ztschr. f. d. ges. Neurol. u. Psychiat. **134**:605, 1931.

44. Lindberg, B. J.: Experimental Studies of Colour and Non-Colour Attitude in School Children and Adults, Especially with Regard to Its Condition in Different Types According to Individual Psychology of Sjöbring and Anthropometric Index of Strömgren, Together with Two Psychological Tests, Acta psychiat. et neurol., 1938, supp. 16, pp. 1-170.

45. Werthheimer, F. I., and Hesketh, F. E.: Significance of Physical Constitution in Mental Disease, Medicine **5**:375, 1926.

46. Cohen, J. I.: Determinants of Physique, J. Ment. Sc. **84**:495, 1938.

builds carry different disease potentialities and disease immunities. As Draper [47a] put it, the "physical features express in the morphologic panel certain basic hereditarial influences." It is with these basic disease potentialities and immunities that the astute physician should be familiar in order to help unravel the mystery of hypertension and other equally elusive diseases. Before the medical profession can truly understand the degenerative diseases it will be necessary to relate them to morphologic physiology and personality and to study man as a whole together with his new environmental surroundings. The study of types of body build is only the beginning. Draper [47b] stated: "In itself, the study of human morphology adds perhaps but little; as a means to the larger conception of the man as a whole, it is well nigh indispensable."

This approach would suggest that the study of hypertension does not belong to the province of any one division of medicine but is a problem of the whole of clinical medicine. Hypertension is not an isolated degeneration that strikes a chance selection of persons after their fortieth year. It is a slow insidious degenerative and metabolic change, "an important morbid state of the body" confined for the most part to a predisposed type. Since hypertension is rare in many primitive tribes it would seem that it appears after the susceptible person has exposed himself for a sufficiently long time to the harmful environmental influences inherent in civilized life, the outstanding one of which is sedentary living.

SUMMARY AND CONCLUSIONS

A review of the literature shows that no rigidly controlled statistical study on a sufficiently large series has conclusively established a positive correlation between blood pressure and body build. Some writers contend that no correlation whatsoever exists.

In this study of blood pressure and body build, made on 3,658 persons, an index derived from dividing the chest circumference by the standing height was used as a ratio of width to height to distinguish the narrow linear type of persons from the broad lateral type.

Among 1,861 men and 1,797 women, 17 per cent of the men and 31 per cent of the women were of the narrow-chested, linear type of build while 12 per cent of both men and women were of the broad-chested lateral type of build.

Observations lead both to the general conclusion that a positive correlation between body build and blood pressure does exist and to the following specific conclusions:

In both men and women there is an increase in the average build—chest/height ratio—with an increase in age. This increase in the adult

47. (*a*) Draper, G.; Dunn, H. L., and Seegal, D.: Studies in Human Constitution: I. Clinical Anthropometry, J. A. M. A. **82**:431 (Feb. 9) 1924. (*b*) Draper, G.: Disease and the Man, New York, The Macmillan Company, 1930.

is greatest before the age of 50 years; after this age there is a tendency for the average build to decrease.

Men and women of lateral, or broad build show a marked tendency to hypertension. The mean, median and modal systolic and diastolic blood pressures increase with an increase in chest/height ratio.

The lateral, broad-chested type of men have more than four times the expectancy of systolic hypertension developing and seven times the expectancy of diastolic hypertension developing as have the men of linear, or slender, build. The women of lateral build have almost eleven times the expectancy of systolic hypertension developing and eight times the diastolic hypertension developing as have the women of linear build.

The men and women of lateral build have only about one-half the expectancy of having a low systolic or diastolic pressure as have men and women of the linear, or slender, build.

In any random group of men of lateral build the ratio of high systolic and diastolic pressures is three times that of low pressures. In any random group of women of lateral build the ratio of high systolic pressure is five times greater than that of low systolic pressures, and the ratio of high diastolic pressure is four times greater than low diastolic pressure.

In any random group of men of linear build the ratio of low systolic pressure is three times that of high pressure and the ratio of low diastolic pressure is five times that of high pressure. In the group of slender women the ratio of low to high systolic or diastolic pressures is 4:1.

In any random group of persons with systolic hypertension the ratio of lateral to linear builds will be: for the men, 4:1; for the women, 11:1. In any random group of persons with diastolic hypertension the ratio of lateral to linear builds will be: for the men, 7:1; for the women, 8:6.

In any random group of persons with low systolic pressures the ratio of linear to lateral builds for both men or women will be more than 2:1. In those with low diastolic pressure the corresponding ratio for men will be more than 2:1 and for women, almost 2:1.

The relation between lateral build and hypertension and between linear build and low blood pressure is found in all age groups.

The incidence of high pressures increases and low pressures decreases with age in men of lateral build. In those of linear build the incidence of high pressure is constant up to the seventh decade; the incidence of low pressure is constant throughout life.

The incidence of high pressures increases with age more markedly among women of lateral build than among those of linear build, and at every age the incidence of low pressure is greatest among the women of linear build.

DIAGNOSIS AND TREATMENT OF GONORRHEAL SEPTICEMIA AND GONORRHEAL ENDOCARDITIS

JOHN STAIGE DAVIS JR., M.D.
NEW YORK

A discussion of gonorrheal endocarditis and gonococcemia seems timely for three reasons:

1. There is increased interest in the disease; the large number of recent papers on the subject have made physicians aware that the condition is by no means uncommon. It has been said to comprise 11.6 per cent of all cases of bacterial endocarditis,[1] and one report stated that of cases of acute endocarditis studied at autopsy 26 per cent were of gonococcic origin.[2]

2. At present the diagnosis is either missed or not made until the disease, the mortality of which is extremely high, has been rampant for several weeks. It may be well to call attention to certain aids in diagnosis in the hope that the physician may at least suspect the presence of the condition before a blood culture positive for gonococci is obtained.

3. The introduction of fever therapy and the use of sulfanilamide and its derivatives have given means with which to combat gonorrheal infections successfully. It is possible that early diagnosis and proper treatment may reduce the mortality in this the most serious complication of gonorrhea.

Fourteen cases are here reported. In 12 of these the diagnoses were proved at autopsy. In the other 2 cases the disease was not fatal; the presence of endocarditis was not proved, nor was the organism ever obtained from the blood stream. However, the evidence in favor of the diagnosis of gonococcic carditis was so strong that it is felt the cases should be included here. These are cases of precisely the type in which diagnosis should be made early so that specific treatment may be initiated promptly.

Read in part before the Section of Medicine of the New York Academy of Medicine May 17, 1938.

1. Thayer, W. S.: Cardiac Complications of Gonorrhea, Bull. Johns Hopkins Hosp. **33**:361, 1922.

2. Williams, R. H.: Gonococcic Endocarditis, Arch. Int. Med. **61**:26 (Jan.), 1938.

In 2 cases the patients were seen by me; the records of other cases were obtained through members of the staffs of St. Luke's, Bellevue, Presbyterian, New York and the New York Post-Graduate hospitals and the University of Virginia Hospitals. Data for 8 other cases of the disease recorded at the Mount Sinai Hospital are abstracted briefly in a separate table. Most of these 8 cases have been previously reported by Newman [3] and others.

One case of probable gonococcemia occurring forty years after the initial infection is also summarized. The patient was recently discharged from St. Luke's Hospital, to which he was admitted with a diagnosis of acute rheumatic fever.

In Cecil's textbook of medicine it is stated by George Blumer [4] that recovery from gonorrheal septicemia occurs occasionally, and there are cases on record in which there was recovery from apparently obvious cardiac complications; but such cases are exceptional. Libman [5] stated that while acute bacterial endocarditis is said to be fatal in all cases, he had gained the impression that acute gonococcic endocarditis had a better prognosis. Warfield,[6] on the other hand, expressed the belief that recovery could not take place in a case of true gonococcic endocarditis.

Friedberg [7] reported 4 cases of gonococcemia, in 1 of which gonorrheal endocarditis was probably also present. All of his patients recovered. He pointed out the importance of correct diagnosis and gave a table of what he considered important points in the differential diagnosis.

My report is presented not so much because 4 of the patients recovered but because I believe that it points out certain aids to diagnosis. The patients who recovered were not proved definitely to have gonorrheal septicemia. However, the evidence in favor of this diagnosis was so strong that it is felt there can be little doubt concerning it.

Jagić and Schiffner,[8] and others [9] have expressed the opinion that mild gonorrheal sepsis may occur with endocardial involvement and, not

3. Newman, A. B.: Prognosis in Gonococcal Endocarditis: Review of Literature and Report of a Case with Spontaneous Recovery, Am. Heart J. **8**:821, 1932.

4. Blumer, G., in Cecil, R. L.: A Text-Book of Medicine, Philadelphia, W. B. Saunders Company, 1927.

5. Libman, E.: Affections of the Valves of the Heart, M. Clin. North America **1**:580 1917.

6. Warfield, L. M.: Gonorrheal Endocarditis, Wisconsin M. J. **20**:578, 1921-1922.

7. Friedberg, C. K.: Gonococcemia with Recovery, Am. J. M. Sc. **188**:271, 1934.

8. Jagić, N., and Schiffner, O.: Ueber gonorrhoische Herzerkrankungen, Med. Klin. **16**:976, 1920.

9. Baker, B. M., Jr., and Carter, E. P.: Three Instances of Unusual Gonococcal Infection, Bull. Johns Hopkins Hosp. **50**:57, 1932.

infrequently, may be followed by complete recovery. They stated the belief that it was not necessary to isolate the organism from the blood stream to make the diagnosis.

The data for the 14 cases of gonorrheal sepsis that I have studied are given in table 1. Thirteen were thought to be cases of endocarditis and 1 was a case of pericarditis. Four cases are reported in detail: cases 6 and 7, in which death ensued, and cases 10 and 14 in which there was recovery.

REPORT OF CASES

CASE 6.—L. F., a man, was admitted to the New York Post-Graduate Hospital on Sept. 13, 1934 because of fever, malaise and articular pain of four weeks' duration. There was no history of gonorrhea or of previous heart disease. On his admission a systolic murmur was heard at the base of the heart; three days later a diastolic murmur was noted in the same region. On October 5 a systolic murmur was heard at the apex, and a notation was made to the effect that the

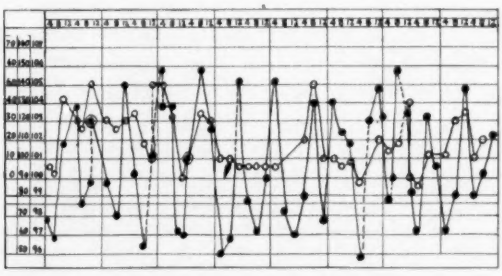

Fig. 1 (case 6).—Temperature (solid circles) and pulse (clear circles) recordings.

murmurs were becoming rougher and louder. Nine blood cultures were sterile. The character of the temperature and pulse curves are shown in figure 1. It is worthy of note that there were two peaks daily for both curves, a point regarded by some physicians as of diagnostic importance. The gonococcus complement fixation was reported as doubtful, and a second specimen was requested. A positive blood culture was obtained on September 9, the organism being reported as the meningococcus; but on October 9 it was finally identified as the gonococcus. A presystolic murmur was heard on October 12. The spleen and liver were both palpably enlarged. Throughout his illness the patient complained from time to time of nausea and vomiting. Petechiae appeared at intervals. The electrocardiogram showed evidence of slight myocardial change. One transfusion of whole blood was given. The patient died on October 16. Autopsy revealed acute vegetative gonorrheal endocarditis of the pulmonary valve, subacute pericarditis and healed endocarditis of the mitral and tricuspid valves. The diagnosis was made eight weeks after the onset of symptoms.

CASE 7.—F. C., a married woman 28 years old, was admitted to the New York Post-Graduate Hospital on Jan. 16, 1931. She complained that chills, fever, night sweats and much pain had been present irregularly for two weeks.

TABLE 1.—*Data on Fourteen Cases of Gonorrheal Sepsis*

Case Number	Number Weeks After Onset Diagnosis Made	History of Heart Disease	Number of Hospital Admissions	Petechiae Present	Gonococcus Complement Fixation	Variation in Murmurs	Spleen Palpable	Pneumonia	Abdominal Pain	Prominent Digestive Disturbance	Streptolysin Titer	History of Gonorrhea	Pleural Effusion	Number of Negative Blood Cultures	Blood Cultures Positive
1	8	None	1	No	Positive	Yes	Yes	Yes	No	Yes	Not done	Yes	No	0	Yes
2	9	Yes	1	Yes	Positive	No	Yes	No	No	No	Positive	Yes	No	0	Yes
3	9	Yes	1	No	Positive	Yes	No (ascites)	No	Yes	Yes	Not done	No	Yes	3	Yes
4	12	None	3	No	Positive 2 times	Yes	Yes	Yes	Yes	Yes	Negative	Yes	No	5	Yes (post mortem)
5	12	None	2	No	Not done	Yes	Yes	Yes	Yes	Yes	Not done	Yes	No	3	Yes
6	8	None	1	Yes	Doubtful	Yes	Yes	No	No	Yes	Not done	No	No	9	Yes
7	18	None	2	Yes	Not done	Yes	Yes	No	Yes	Yes	Not done	No	No	4	Yes (post mortem)
8	4	Yes	1	No	Not done	Yes	Yes	Yes	No	No	Not done	No	No	2	Yes (post mortem)
9	8	Yes	1	No	Not done	Yes	Yes	Yes	Yes	Yes	Not done	Yes	No	5	Yes
10	4	None	2	No	Positive	Yes	No	No	Yes	Yes	Not done	Yes	No	8	No organism obtained from joint
11	4	None	1	Yes	Not done	Yes	Yes	No	No	Yes	Not done	No	No	1	Yes
12	11	Yes	2	No	Not done	Yes	Yes	Yes	Yes	Yes	Not done	No	Yes	3	Yes
13	3	Yes	1	No	Not done	Yes	No	Yes	Yes	Yes	Not done	No	Yes	2	Yes (post mortem)
14	14	None	2	No	Positive 9 times	Marked	Yes	5 times	Yes	Yes	Not done	Yes	Cloudy	9	No
Average of total	9	6	1.5	4	7 positive; 7 not done	13	11	8	9	12		7	4	54	12
Percentage of all cases	43			29		93	79	57	64	86		50	29		86

She had been discharged from St. Luke's Hospital on Nov. 12, 1930, with a questionable diagnosis of acute pyelitis. There was only a slight amount of pus in the urine. The spleen was palpably enlarged. On one occasion, while she was at St. Luke's Hospital, it was thought the patient might have pneumonia in view of the presence of fever (103 F.) and severe pain in the chest. After leaving this hospital she was never entirely well; at irregular intervals she was harassed by chills and sweats. At the New York Post-Graduate Hospital a few petechiae and varying cardiac murmurs were noted, and splenomegaly was found. There was no evidence of pneumonia. A gonococcus complement fixation test was not done. Nausea and vomiting were prominent symptoms; occasionally there was some abdominal pain. Four blood cultures were sterile. At the time of death, eighteen weeks after the onset of symptoms, a diagnosis of subacute bacterial endocarditis due to Streptococcus viridans was made, and it was apparently confirmed at the postmortem examination. The true nature of the condition was discovered only after sections of the heart valves had been studied.

Case 10.—V. Y., a woman aged 21, was admitted to the Bellevue Hospital on Sept. 14, 1934; she complained of pain, of three days' duration, in the left side of the chest, and in the left knee and wrist. She had been exposed to gonorrhea two months before and had had local treatment during the month preceding admission. There was no history of previous heart disease. There were soft systolic murmurs heard at the apex of the heart and at the base on admission; these did not change. The temperature was 101.5 F. on admission. Two days later she had chills and fever. The precordial pain was severe, and a loud pericardial friction rub could be heard. The urethral smear was positive for gonococci. The results of the gonococcus complement fixation test were now positive, although at first negative results had been obtained. Eight blood cultures were sterile. At no time was the spleen palpable. There was no evidence of pneumonia, and there were no petechiae. A diagnosis of gonorrheal pericarditis, arthritis and septicemia was suggested at the onset. Five days after the friction rub had become apparent the patient was given a bout of fever therapy. After six hours at a temperature between 106 and 107 F., she improved. The friction rub almost disappeared, but it reappeared loudly the following day. For the next month she had pains in the joints and pelvis, leukorrhea, low grade fever, precordial pain and nausea. She was then given a second bout of fever therapy, after which her recovery was uneventful. The urethral smears became negative, the friction rub disappeared and the results of gonococcus complement fixation test were negative. At the time of the patient's discharge, seventy-six days after admission, the electrocardiogram was normal; previous tracings had shown changes.

Case 14.—R. K., a married man 41 years of age, was admitted to St. Luke's Hospital on Dec. 13, 1935. In September a low grade fever had developed which continued, on and off, for about six weeks. He had some indigestion and felt as if he had a cold; however, he had no cough, sore throat or pain in the chest and was not ill enough to go to bed. He thought that the drinking of a moderate amount of ale had been the cause of his abdominal distress. This first illness was followed by a period of about six weeks during which he had no complaints and no fever.

On November 1, while he was in Berlin, he became nauseated and vomited just after drinking some rather poor wine. That night his temperature was 102 F. The fever continued irregularly (99 to 102 F.) during the next two and

a half weeks. During this period he went to Paris, where he was told he had pneumonia and was sent to bed. At no time during the illness did he feel particularly sick.

By December 1 his temperature was normal and he was allowed to return to the United States. While at sea, he drank champagne and afterward he again became nauseated and vomited. The next day his temperature was again 102 F.; the pulse rate was 100, and the respiration was 26. Physical examination on admission to St. Luke's Hospital revealed no other abnormalities, except for a low-pitched nontransmitted systolic murmur at the base of the heart. The blood pressure was 120 systolic and 85 diastolic. A blood count showed 8,400 leukocytes and 4,900,000 red blood cells. The sedimentation rate was 44 mm. in one hour. There was no urethral discharge, and prostatic examination showed no abnormalities. Several teeth appeared to be devitalized. The only important particulars in the past history were the facts that during the previous three months the patient had

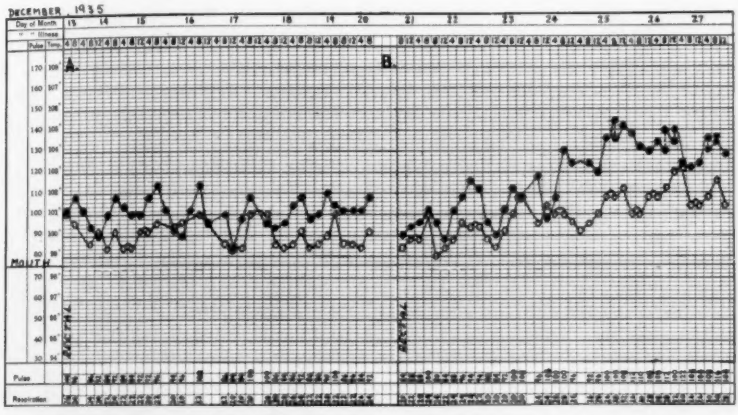

Fig. 2 (case 14).—*A*, temperature (solid circles) and pulse (clear circles) recordings during first eight days in hospital. *B*, temperature (solid circles) and pulse (clear circles) recordings from Dec. 21 to 27, 1935.

traveled in Italy, Spain, Germany and France and had eaten and drunk in various types of places and that twenty years before he had had a case of severe gonorrhea. During the few nights before the onset of the acute illness, he had been on something of a sexual and alcoholic debauch. During the first nine days of his stay in the hospital, the temperature varied from 99.4 to 102.2 F. Its course in the first eight days is shown in figure 2 *A*. A roentgenogram of the chest on December 14 was negative; agglutination tests for typhoid and undulant fevers were negative, and the blood culture was sterile.

The blood count on December 19 showed 5,300,000 red cells and 10,800 leukocytes, of which 22 per cent were lymphocytes, 73 per cent were polymorphonuclear neutrophils, 1 per cent were eosinophils and 5 per cent were monocytes.

The complement fixation test for gonococcus was positive on December 13. A gastric analysis on December 21 gave normal results. A roentgenogram taken of the sinuses on December 16 showed them to be clear. On December 17 a roentgeno-

gram of the teeth showed large abscesses which involved the central and lateral incisors on the upper left side and beginning absorption at the apex of the central incisor on the upper right side and of the central incisor on the lower left side. Gastrointestinal studies on December 16 and 20 gave negative results. Two teeth were extracted on December 19; during the following two days the temperature was slightly lower, but on December 22 it began to rise and by December 25 it had reached 105 F. This phase of the illness is shown in figure 2 *B*.

A roentgenogram of the chest on December 26 showed early consolidation and evidence of fluid at the base of the right lung. A blood culture taken on December 24 was sterile. The sputum at this time was blood streaked and contained many spirochetes and a few pneumococci which could not be typed. The leukocyte count was 23,800 with 86 per cent polymorphonuclear cells. A specimen of urine was normal except for a faint trace of albumin. An electrocardiogram done on December 24 was reported as normal (fig. 3).

During the second week in the hospital the patient was given intradermal injections of a nonspecific milk preparation (aolan) every second day. On December 26, 20 cc. of cloudy thick fluid was removed from the chest by aspiration. A

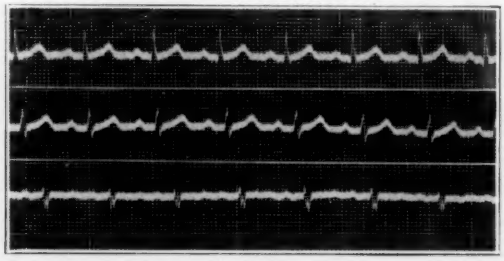

Fig. 3 (case 14).—Electrocardiogram taken on Dec. 14, 1935.

cell count of the fluid showed 11,750 leukocytes per cubic centimeter, with 88 per cent polymorphonuclears and 12 per cent lymphocytes. No growth was obtained on culture of this fluid. Smear cultures were negative for organisms. Inoculation of guinea pigs gave negative results. No spirochetes could be found. The sputum was negative for tubercle bacilli on December 27.

On December 27, 10 cc. of clear fluid was removed from the chest. On Jan. 5, 1936, 10 cc. of clear straw-colored fluid was removed. By this time the patient, who had been irrational for one week, was again rational, and the temperature had fallen somewhat. During this time he was slightly jaundiced. The urine contained urobilin but no bile. Aspiration was again done on January 8; only 5 cc. of blood-tinged, sterile fluid could be obtained. During the next week his condition remained unchanged. On January 15 he again had pneumonia. Pneumococci of type XXVII were cultured from his sputum. No gonococci could be found. His temperature curve during this period is shown in figure 4.

On January 19, at the suggestion of a consultant, a twelfth rib was removed and the diaphragm and liver inspected, without opening the pleural cavity. No pathologic changes were demonstrable. After the operation the fever continued until March 6. The temperature curve for part of the period after operation is shown in figure 4. During this time the patient had two more attacks of

pneumonia. In all, he had pneumonia four times. Roentgenograms taken on these occasions are shown in figure 5. In table 2 are shown the blood counts and sedimentation rates.

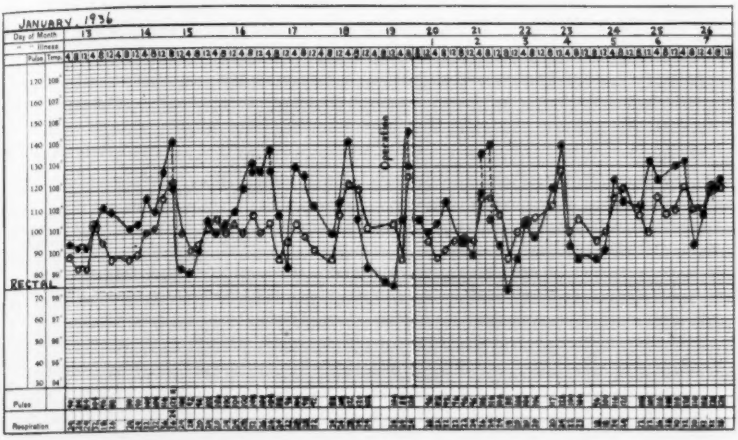

Fig. 4 (case 14).—Temperature and pulse recordings, before operation, on Jan. 19, 1936, and after operation.

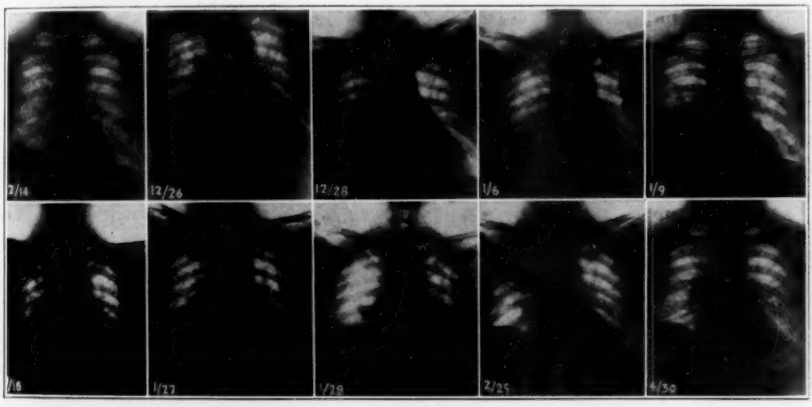

Fig. 5 (case 14).—Roentgenograms taken during course of attacks of pneumonia.

Nine blood cultures done on various occasions with various kinds of mediums were sterile. Miss Margaret Straub, of the New York Post-Graduate Hospital, made some special cultures for gonococci but was unable to obtain any growth.

At no time were there any petechiae. The character, intensity and location of the murmur changed from day to day. On three occasions gallop rhythm developed. The electrocardiogram done on March 2 is reproduced in figure 6. In figures 7 and 8 are shown the electrostethographs taken March 10 and April 30, 1936.

The patient was given eleven transfusions of whole blood, but it was not until these were administered every two days that any benefit was noted. He also was given Corbus-Ferry gonococcus filtrate intradermally.

He left the hospital on March 14 in an ambulance; he was not allowed to get up until April 1.

TABLE 2.—*Laboratory Data for Case 14*

Date	Hemoglobin, per Cent	Red Blood Cells	White Blood Cells	Differential			Sedimentation Rate	Gonococcus Complement Fixation
				Neutrophils	Lymphocytes	Eosinophils		
12/13/35	93	4,900,000	8,400	74	21	..	44	+
12/14/35	..	.....	12,800	84	16	..	..	..
12/18/35	..	.....	.....	..	..	..	..	+
12/19/35	93	5,300,000	10,800	72	27	1	..	..
12/24/35	100	4,100,000	23,800	84	14	2	..	..
1/11/36	66	3,800,000	11,300	86	14	..	..	..
1/20/36	74	4,670,000	18,800	60	40	..	..	..
1/28/36	81	4,620,000	17,900	92	8	..	..	..
2/ 5/36	79	4,220,000	.....	..	..	..	..	..
2/13/36	..	.....	.....	..	..	..	..	..
2/25/36	57	5,500,000	22,800	78	22	..	..	..
3/ 6/36	64	6,050,000	11,400	76	24	..	..	..
3/ 9/36	76	.....	.....	..	..	..	..	..
3/11/36	76	5,400,000	9,400	76	24	..	..	..
3/13/36	..	.....	.....	..	..	..	40	+
3/21/36	96	5,100,000	.....	..	..	..	31	..
3/24/36	..	.....	.....	..	..	..	..	+
3/31/36	..	5,100,000	19,800	..	..	..	..	+
4/ 4/36	..	.....	.....	..	..	..	60	..
4/ 9/36	..	.....	.....	..	..	..	..	+
4/18/36	..	.....	.....	..	..	..	30	..
5/ 2/36	..	.....	.....	..	..	..	12	..
5/28/36	..	.....	.....	..	..	..	..	+
6/ 1/36	..	.....	.....	..	..	..	12	+
7/ 8/36	..	6,500,000	12,000	..	..	..	9	..
8/14/36	113	5,500,000	9,400	43	57	..	8	+

On April 12 his temperature began to rise again, and he was given another transfusion. He was allowed to walk on May 15. By June 1 he was feeling well and had gained about 20 pounds (9 Kg.). The pulse rate averaged 84, and the diastolic murmur had disappeared. The sedimentation rate was normal.

Comment.—This case is reported in some detail because of certain unusual features and because of the recovery in what seemed to be, but was not entirely proved to be, a case of gonococcic endocarditis. Friedberg[7] stated that the symptoms which are specifically referable to endocardial involvement consist essentially of embolic phenomena and alteration in heart sounds.

A case reported by Perry[10] in 1930 is so similar to this case that a brief summary of it seems fitting. His patient recovered after seventy-

10. Perry, M. W.: Gonorrheal Endocarditis with Recovery: Case Report, Am. J. M. Sc. **179**:599, 1930.

three days in the hospital, during which period he had pneumonia three times (pulmonary emboli). There was a systolic murmur, which later became diastolic, over the area of the pulmonary valve. There were no petechiae. The patient's feeling of well-being was out of proportion to his symptoms. He received fourteen blood transfusions (each of 250 cc. of citrated blood) and 150 cc. of immune serum. He was also

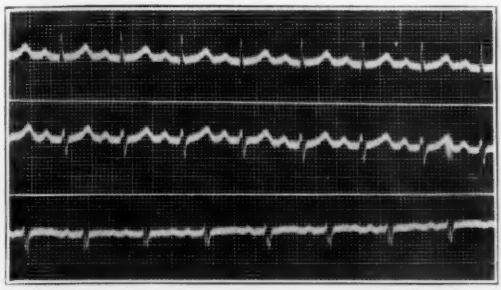

Fig. 6 (case 14).—Electrocardiogram taken on March 2, 1936.

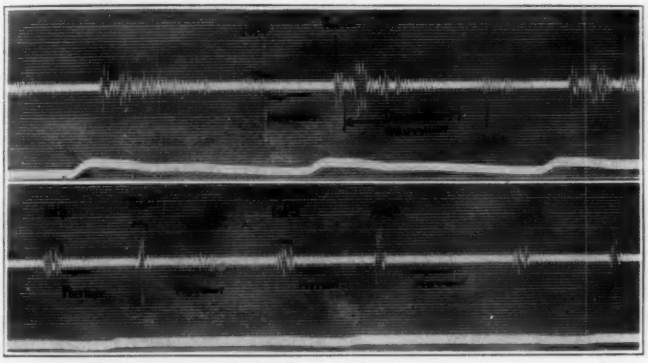

Fig. 7 (case 14).—Electrostethograph taken on March 10, 1936.

given gonococcus vaccine. In this case, however, gonococci were found both in the urethral smear and, finally, after repeated cultures, in the blood stream. In my case, I was not able to obtain the organism. In 1933 Perry [11] gave a follow-up report on his case and noted that the patient seemed well, and the electrocardiogram showed no abnormalities. The diastolic murmur, however, still persisted.

11. Perry, M. W.: Further Note on Case of Gonorrheal Endocarditis with Recovery, Am. J. M. Sc. **185**:394, 1933.

Since I was unable to demonstrate the gonococcus in my case, it might be argued that the diagnosis was not correct; but the following points appear to substantiate it:

1. The gonococcus complement fixation test was positive nine times. There are many who will say that this test has been largely discredited; for example, the New York Board of Health stopped using it as a routine measure. This opinion, however, is fast giving way, and the test, as now done, is accurate to a fairly high degree. Recently Barringer expressed the view that the test is one of the most valuable in medicine.[12]

2. There were no petechiae.

3. The heart murmurs varied from day to day.

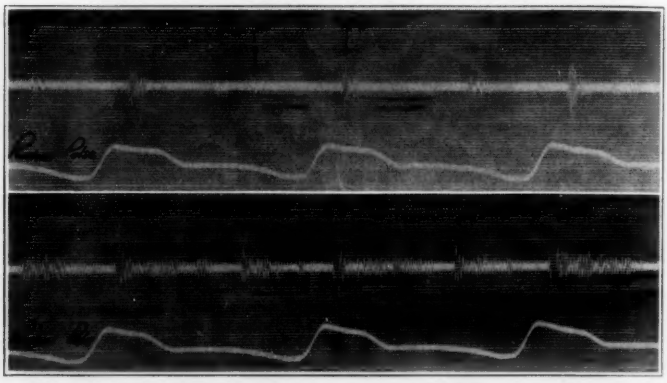

Fig. 8 (case 14).—Electrostethograph taken on April 30, 1936.

4. There was no change in conduction time of the heart, such as would be expected in a rheumatic infection. Levy and Turner [13] stated that disturbances in auriculoventricular conduction time are found more often in rheumatic fever than in any other disease. In endocarditis due to the gamma nonhemolytic streptococcus and in subacute bacterial endocarditis due to the viridans (alpha) electrocardiographic changes are uncommon. Sabathié,[14] however, has stated that one type of gonorrheal endocarditis, which he termed "la myo-endocardite gonococcique,"

12. Barringer, E. D.: Complement Fixation Test: A Diagnostic Aid in the Control of Gonorrhea, New York State J. Med. **38**:699, 1938.

13. Levy, R. L., and Turner, K. B.: Impaired Auriculoventricular Conduction in Rheumatic Fever, Arch. Int. Med. **43**:267 (Feb.) 1929.

14. Sabathié, L. G.: La myo-endocardite gonococcique. Sa pathogénie, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:610, 1935.

is associated with electrocardiographic changes, and that these changes are due to involvement of the intraventricular bundle. In this type there are no embolic phenomena, and valvular involvement is late and not as significant.

5. After bouts of pneumonia, in which there had been sustained fever, there would be a period during which the patient had a comparatively low temperature, which probably indicated that the invading organism was sensitive to heat; such sensitivity is characteristic of the gonococcus. Some writers invoke the theory that the extreme thermolability of the gonococcus is responsible for cases of gonorrheal sepsis in which there is spontaneous remission. For this reason, in this instance it had been suggested that the patient be blanketed when his temperature reached 106 F., and that an attempt be made to keep his temperature at this level for several hours in an effort to kill the gonococci. However, I was diffident and this measure was not tried.

6. The cloudy fluid removed from the cavity in the chest was apparently sterile; similar observations are made in gonorrheal pleurisy.[15]

7. The history included a severe attack of gonorrhea twenty years before and recent alcoholic and sexual excess.

8. Recovery followed multiple blood transfusions and the administration of Corbus-Ferry filtrate.

9. The patient had five attacks of pneumonia which was probably embolic.

10. Jaundice was present; however, it was most probably due to hemolysis.[15a]

11. The spleen was palpable.

12. Gallop rhythm was noted on three occasions.

13. The patient suffered from such severe abdominal pain (probably embolic in character) that an exploratory operation was performed.

Ross and Greaves[16] reported 2 cases of gonorrheal endocarditis proved at autopsy. In 1 there was an embolic pneumonia. In the other the diagnosis was not made for some time after the onset of the disease; the appendix, which was removed because of abdominal pain, tenderness and rigidity, was normal. The authors stated the belief that the abdominal symptoms had been embolic in origin. No petechiae were seen in either case.

15. Pratsicas, A.: Contribution a l'étude des manifestations viscérales de la gonococcie (endocardite, pneumonie), Paris méd. **1**:521, 1928.

15a. Tice, F.; Friedenwald, J., and Warren, L. F.: The Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1932.

16. Ross, C. W., and Greaves, F. C.: Gonococcic and Meningococcic Endocarditis with Report of Three Cases, U. S. Nav. M. Bull. **33**:179, 1935.

14. There was evidence of renal infarct (blood and casts in the urine). In this connection it is interesting to note that in this disease death is often of renal origin.[17]

COMMENT

In certain cases, such as those in which the acute disease follows trauma to the urethra in the course of treatment of acute gonorrhea, the diagnosis is simple. It is not relative to this type of case that this paper is written. However, it seems fitting to call attention to such cases, because if my findings are kept in mind an earlier diagnosis may be made, which will prevent useless major operations and explorations of the chest and will hasten the patient's recovery. Moreover, it would appear that if sulfanilamide or fever therapy could be used early in the disease the mortality could be much reduced.

TABLE 3.—*Data for Cases Recorded at Mount Sinai Hospital*

Case No.	No. Weeks After Onset Before Diagnosis	History of Heart Disease	Admitted 2 or More Hospitals	Petechiae Present	Gonococcus Complement Fixation	Variation in Murmurs	Spleen Palpable	Pneumonia
15	4	No	No	Yes	Negative	Yes	Yes	No
16	32	No	No	Yes	Not done	Yes	No	No
17	1½	No	No	Yes	Yes	Yes	Yes	No
18	5	No	No	Yes	Not done	Yes	Yes	Yes(1)*
19	8	No	No	No	Yes	Yes	Yes	No
20	14	No	No	Yes	Yes	Yes	Yes	No
21	2½	Yes	No	Yes	Negative	Yes	Yes	Yes (1)
22	8	Yes	No	Yes	Not done	Yes	No	Yes (1)

* The patient had one attack.

The cases recorded at Mount Sinai Hospital are summarized in table 3. Several of these cases have been reported by Newman[3] and by Friedberg.[7] Case 20, in which recovery took place, was reported in detail; the final diagnosis was gonorrheal endocarditis.

Williams[17] has recently reported 2 cases of gonorrheal endocarditis which are of interest. In the first case there was no previous history of gonorrhea, and the diagnosis was not made until the patient had been acutely ill for five weeks. The first three blood cultures were negative; the fourth, fifth and sixth, done over a period of fifteen days, were positive. Although this patient had serious renal and hepatic disease, he was placed in the Kettering hypertherm. After one fever treatment his blood became sterile. Unfortunately, the patient became anuric, although he seemed to bear the treatment well. He was given a second fever treatment, which was well tolerated. The next day he died of renal insufficiency. It may be stressed that gonorrheal sepsis

17. Williams, R. H.: Gonococcal Endocarditis Treated with Artificial Fever (Kettering Hypertherm), Ann. Int. Med. **10**:1766, 1937.

can, of itself, produce marked renal damage and cause uremia. The interesting and important features are that after the fever treatment the gonococcemia disappeared ante mortem and that the blood and the gonococcic vegetation in the heart were sterile on postmortem examination. The possibility that fever treatment may have intensified the manifestations of uremic intoxication was considered, but the necropsy threw no light on this. The second case reported by Williams was one of gonorrheal septicemia which developed in a man aged 46 twenty years after an attack of gonorrheal urethritis. The patient had been told eight years before that he had a "slightly leaking heart valve." It was unusual that one of his first symptoms was the appearance of petechiae. He also had a mitral murmur which changed in quality and in intensity. There were slight electrocardiographic changes, which were interpreted as being due probably to transient myocardial disease (questionable embolism). Four blood cultures were negative. Gonococci could not be demonstrated in the urethral or prostatic secretion. Two weeks after admission, or five weeks after the onset of symptoms, the right ankle became swollen, painful and tender; pus aspirated from it contained gonococci. Twenty-four days after admission it was decided that the patient had gonorrheal endocarditis, and he was given three treatments in the Kettering hypertherm. The temperature was maintained between 105 and 106 F. for five hours, and on one occasion it rose to 108.2. After the first treatment his temperature returned to normal, and it remained practically normal thereafter. The mitral murmur became less harsh. Six months later, the results of the follow-up examination were essentially normal except that a faint systolic murmur was heard at the area of the mitral valve. The sudden onset of this patient's illness, with a chill and high fever; the presence of numerous large petechiae with areas of central necrosis; the high, septic fever with occasional chills; the transient multiple arthritis, with subsequent development of acute purulent monarticular arthritis from which gonococci were obtained; the presence of transient electrocardiographic alterations indicating acute changes in the myocardium, and the change in character of the apical murmur constitute convincing evidence of severe (metastatic) gonococcic infection, and they strongly suggest that gonococcic endocarditis was present.

In a recent article, Williams [2] reported 12 cases of fatal gonorrheal endocarditis seen at the Vanderbilt University Hospital. He emphasized the importance of the disease, and stated that it is not rare, since it was present in 26 per cent of the patients with bacterial endocarditis (acute and chronic) at the Vanderbilt University Hospital. He stated that careful observation and thorough laboratory examinations will lead to a correct diagnosis and that although the prognosis is grave the use of the Kettering hypertherm and sulfanilamide offers some hope.

Thayer [1] stated that gonorrhea is an infection which is focal at first but which spreads not only by direct extension but also, and not infrequently, through the blood stream. In the latter case there is a general septicemia associated with a variety of metastases—notably arthritis, synovitis and myositis and not infrequently endocarditis, myocarditis or pericarditis. Of 176 instances of acute endocarditis of determined origin, 11.3 per cent were gonococcic. Thayer stated that "gonorrheal cardiac infections as a whole are by no means very unusual." In his series, involvement of the pulmonary orifice was fairly common, but the aortic valves were most commonly involved. The duration of the disease was usually from four to nine weeks.

In 1933 the Welfare Council of the Works Progress Administration made a survey of the diagnoses of all the patients admitted to New York hospitals during that year. There were 567,000 hospital discharge schedules that year. In only 4 of these was a diagnosis of gonorrheal endocarditis recorded, although in 4,540 schedules the diagnosis of gonorrhea of various types was given.

White [18] has stated that gonococcus, Streptococcus haemolyticus, the pneumococcus and Staphylococcus aureus, in equal frequency, are the organisms responsible in nearly 100 per cent of the cases for acute bacterial endocarditis. He also stated that gonorrheal endocarditis is almost invariably fatal.

DIAGNOSIS

In order to furnish assistance in establishing the diagnoses during the delay incident to obtaining positive blood cultures, certain diagnostic points have been gleaned from the cases here reported and from the literature. These are given in the following list:

1. A history of gonorrhea may be noted.

2. Chills and septic temperature may be present. They are less severe if gonococcemia is present without endocarditis.

3. Frequently the temperature curve shows two peaks of fever in one day.

4. After high or sustained fever, such as occurs in embolic pneumonia, the temperature is apt to become nearly normal.

5. The gonococcus complement fixation test, if repeatedly positive, is of great diagnostic value.

6. A positive blood culture is often difficult to obtain. The organism grows more readily in venous blood; hence there is better chance for growth if the culture is kept in an atmosphere of carbon dioxide and if the blood sample is obtained from an artery before the blood has traversed the whole arterial tree.

7. The right side of the heart is more frequently involved than the left, but the site of involvement may vary with the point of origin of the infection.

8. If pneumonia, which is frequently present because of the occurrence of embolism, is present it is more difficult to obtain a positive blood culture because the capacity of the lungs to act as a filter is increased.

18. White, P. D.: Heart Disease, New York, The Macmillan Company, 1934.

9. Sudden abdominal pain is a frequent embolic phenomenon. In 2 of the cases here reported the diagnosis of an acute condition in the abdomen was made, and in 1 of these cases an exploratory operation was done.

10. Renal irritation is often noted; blood, pus and casts may be found in the urine, and death is frequently due to uremia.

11. Cutaneous lesions are sometimes seen; the characteristic lesion is an erythematous macule that acquires a central vesicle or pustule. This is usually seen in gonococcemia without endocarditis.

12. Varying roughened cardiac murmurs—usually diastolic—may be present.

13. Petechiae are not as common as in other types of bacterial endocarditis.

14. The spleen is more apt to be enlarged than in other types of bacterial endocarditis.

15. The electrocardiogram is usually normal, unless pericarditis or abscess is present.

16. The antistreptolysin titer and cutaneous tests with nucleoprotein are negative unless the patient has had rheumatic fever.

17. Arthritis is present in about 50 per cent of the cases.

18. Jaundice is frequently present.

19. The average white cell count is higher than in other types of endocarditis.

20. The symptoms fail to respond to the administration of salicylates.

21. Exacerbation of chills and temperature occurs following prostatic massage.

RÉSUMÉ

From a study of the data collected in this paper, certain points stand out: (1) the difficulty in establishing a definite diagnosis, which is often not made until after death; (2) the frequent occurrence of pneumonia; (3) the infrequency of petechiae and the peculiarity of the cutaneous lesion; (4) the difficulty attendant on obtaining a positive blood culture, and (5) the fact that recovery is possible.

These points will be discussed briefly in order.

Difficulty in Diagnosis.—The condition is rarely thought of unless there is a recent history of gonorrhea. A case observed recently in St. Luke's Hospital illustrates this point:

CASE 23.—The patient, a man 72 years old, had had gonorrhea forty years before. He was admitted to the hospital on April 26, 1938, with a history of having had fever (temperature as high as 106.5 F.) and chills, off and on, for four weeks. Several joints had been swollen and hot; the involvement was migratory. His condition was diagnosed as acute rheumatic fever. He did not respond to the administration of salicylates. A section of the temperature curve while he was at the hospital is given in figure 9. The white cell count was 52,000 on one occasion. No murmurs were heard in his heart. On one occasion, after his temperature had reached 106.6 F., he had a transient hemiplegia. On several occasions he had numerous rales at the bases of the lungs. At one time he was given prostatic massage; he then had a severe chill and his temperature went to 106 F. The gonococcus complement fixation test was positive, with both antigens, on two occasions. Four blood cultures remained sterile. His right

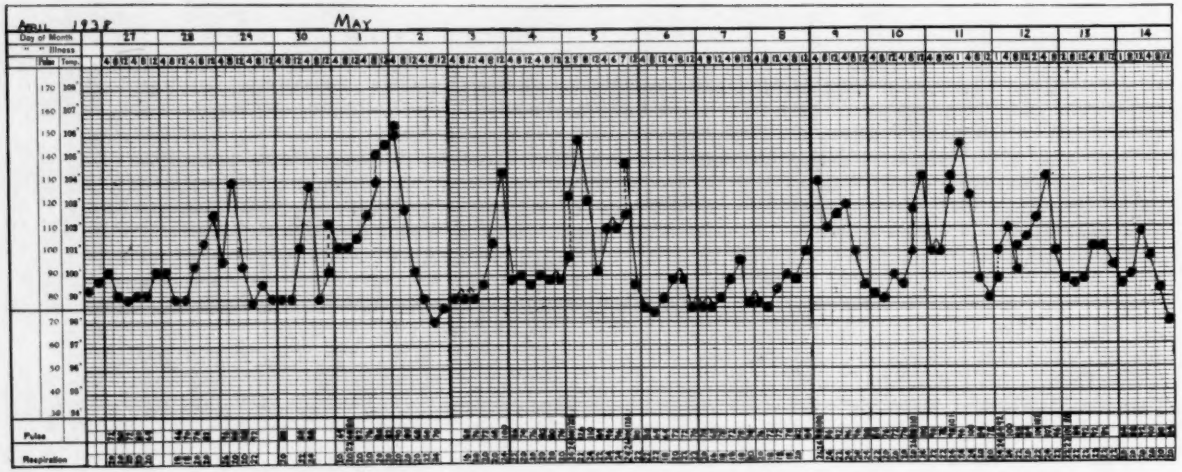

Fig. 9 (case 23).—Section of temperature curve during the patient's stay in the hospital.

knee and wrist had the typical appearance of a joint with a gonorrheal infection. On May 15 the administration of sulfanilamide was begun. On May 17 he was given a transfusion of 500 cc. of whole blood. By May 30 his temperature had been practically normal for ten days, and he was allowed to sit up. Pain and stiffness in the right knee were his only complaints at that time. He was discharged from the hospital on June 16. When last seen he had made a complete recovery and had returned to work.

Frequent Occurrence of Pneumonia.—According to Schottmueller [19] the metastasizing tendencies of bacteria differ. Anaerobic streptococci and Welch bacilli have slight tendency to metastasize, although they circulate freely in the blood. Staphylococci metastasize in most instances. Gonococci produce mostly valvular, articular and cutaneous foci, while meningococci produce, almost exclusively, cardiac, meningeal and cutaneous lesions. Gonococci, pneumococci and meningococci tend to settle especially on the valves of the right side of the heart, indicating, perhaps, that conditions for the multiplication of these organisms are better in venous blood; hence, also, the frequency with which pulmonary infarcts develop. It is estimated that in about 12 per cent of the cases of sepsis the infection is in the form of endocarditis, which is practically always fatal; in about 60 per cent of the cases it is in the form of thrombophlebitis, which has a mortality of 70 per cent, and in about 10 per cent of the cases it is in the form of lymphangitis, with a mortality of 50 per cent.

If bacteria from a thrombophlebitis or some other focus float into the blood stream, they will be arrested in the lungs in either a large branch of the pulmonary artery or in the capillary sieve, depending on their size. There are three possible ways by which they may reach the greater circulation: 1. Bacteria may pass through the open foramen ovale or through the interventricular septum. 2. They may pass through the filter formed by the pulmonary capillaries. (This is possible because blood corpuscles of large size can pass the capillary filter.) However, the sensitized pulmonary capillary bed has tremendous phagocytic power and filters out extraordinary numbers of bacteria. (I am reminded of a case seen by Keil,[20] in which no petechiae developed until just before death, when they appeared in great numbers. This sudden appearance was attributed to failure of the pneumonic lung to act as a filter.) 3. A new focus of infection in the pulmonary circulation receives bacteria-containing plugs which form infected infarcts and suppurating metastases; and such a metastasis may then become connected with the pulmonary vein in the sense of a thrombophlebitis and so bacteria reach the greater circulation through infected thrombotic particles. Therefore, one must assume the existence of a new septic focus.

19. Schottmueller, H.: Treatment of Syphilis of Aorta, Am. J. Syph. **9**:1, 1925.
20. Keil, H.: Personal communication to the author.

In the lung a primary septic focus may develop as, for example, in grip. Fraenkel [21] and others have demonstrated the dissolution of foci into the arteries and veins of the lungs. Wohlwill [22] demonstrated in 21 of 24 cases of metastasizing sepsis the presence of a secondary septic focus in the anatomic area under discussion. This is a high percentage not even surpassed by the demonstration of vascular foci in the form of caseous endangiitis in miliary tuberculosis, in which the pathologic process is essentially the same. As thrombophlebitic sepsis occurs principally in the tributary area of the vena cava, one is dealing mostly with the existence of secondary septic foci in the lungs, namely, in pulmonary veins. Accordingly, blood coming from the infectious focus should contain the greatest numbers of bacteria. If the arterial blood contains more bacteria than the venous blood, a secondary septic focus has arisen either in the lungs or in the heart. It therefore seems advisable to make cultures from the arterial circulation in the greater hope of obtaining one positive for gonococci. Nathan [23] in 28 of 31 cases of metastasizing sepsis in which death occurred noted the presence of thrombophlebitis of the pulmonary vein. Before 1932 this condition was not sought for, as the bacteremia was explained on the basis of the passage of bacteria through the pulmonary capillaries. This theory, of course, rejects the assumption that multiplication of bacteria takes place in the circulating blood.

Nathan [23] reported a case of sepsis secondary to the introduction of a bougie into the urethra in a young man treated for gonorrhea. A prostatic abscess developed, and there was infiltration in both lungs; the clinical picture was that of metastatic sepsis with fever. Autopsy showed thrombophlebitis of the venous plexus of the prostate and the development of pulmonary abscesses from septic pulmonary emboli; in one of these abscesses there was a thrombophlebitis of a larger vein, which constituted the focus through which the infection reached the general circulation.

In 1 patient in my series there was apparently a septic infarct or an embolic abscess near the pleura which ruptured through the latter, producing an empyema. Multiple pulmonary infarcts occurred from a right-sided mural thrombus. A later deeper infarct was accompanied by a serous effusion.

Infrequency of Petechiae and the Peculiarity of the Cutaneous Lesion.—Petechiae are probably less frequent in gonococcemia than in other types of sepsis, because, as stated previously, the organism usually fails

21. Fraenkel, E.: Ueber postanginöse Pyämie, Virchows Arch. f. path. Anat. **254**:639, 1925; Deutsche med. Wchnschr. **53**:93, 1926.

22. Wohlwill, F.: Pathologisch-anatomische Beiträge zum Problem der Sepsis, Arq. de pat. **7**:157, 1935.

23. Nathan, H.: Neuere Gesichtspunkte zur Sepsisfrage, Chirurg **4**:369, 1932.

to get through the pulmonary filter. Other cutaneous lesions are more often seen in gonococcemia. They have been well described by Keil [24] in an article and in a personal communication: [20]

Of the various types of eruption, some are distinctive, but others are banal and therefore are of little help in formulating a diagnosis. As gonococcic endocarditis occurs in but a small percentage of patients afflicted with this form of bacteremia, the cutaneous lesions, for the most part, indicate an infection of the blood stream in the absence of a complicating endocarditis. The recognition of these eruptions is of diagnostic and prognostic importance.

The most distinctive cutaneous lesions in gonococcic bacteremia are:

1. Keratoderma blenorrhagicum and variants. This lesion indicates the presence of bacteremia. So far as I can gather, there are no cases of proved gonococcic endocarditis in which this dermatosis has been observed.

2. Hemorrhagic vesiculopustular and bullous lesions of the skin. The clinical picture is somewhat analogous to that seen in keratoderma blenorrhagicum. However, it seems easier to isolate the organism in these cases. In none of these cases has there been proof of an associated endocarditis. In Massini's [25] case, an isolated one to be sure, postmortem examination showed the heart to be free of abnormalities.

3. Lesions resembling Osler's nodes. The presence of Osler's nodes is uncommon in gonococcic subacute bacterial endocarditis. Occasionally one sees somewhat similar lesions in cases in which there is but little evidence of endocarditis and in which complete recovery seems to ensue. The status of this manifestation is still uncertain, and continued observations appear to be essential before more definite conclusions can be reached in regard to the significance of this lesion.

4. Purpura. This lesion, is occasionally seen; it will always be necessary to eliminate the possibility of a coincidental renal insufficiency or of the presence of jaundice as the cause.

5. Petechial manifestations—localized or diffuse. These may occur in the absence of a complicating endocarditis. Petechiae found as small lesions on the chest, abdomen, conjunctiva and mouth are of greater significance when they show white or pale centers and occur in crops. In such instances they generally indicate the presence of endocarditis. Special significance must be given to cases of right-sided endocarditis due to gonococci characterized by many episodes of pulmonary disease and by petechial lesions that appear late in the course or terminally. I have

24. Keil, H.: A Type of Gonococcal Bacteraemia with Characteristic Hemorrhagic Vesiculo-Pustular and Bullous Skin Lesions, Quart. J. Med. **7**:1, 1938.

25. Massini, R.: Ueber Gonokokkensepsis; gonorrhoisches Exanthem, gonorrhoisches Phlebitis, Ztschr. f. klin. Med. **83**:1, 1916.

seen 1 such case. The clinical picture is essentially the same as in cases of subacute bacterial endocarditis of the right side of the heart due to Str. viridans.

Difficulty Attendant on Obtaining a Positive Blood Culture.—There are three factors in this difficulty: (*a*) The gonococcus is easily killed. (*b*) The cultures should be placed under carbon dioxide so that they will not take up oxygen from the air. (*c*) Few organisms reach the brachial veins, especially when pneumonia is present to increase the capacity of the lung as a filter (petechiae and pneumonia rarely occur at the same time).

Possibility of Recovery.—Three cases of gonorrheal septicemia with endocarditis in which recovery took place have been reported. One of these was a case of pericarditis. In another, the gonococcus was never

TABLE 4.—*Data on Three Cases of Gonococcic Endocarditis with Recovery*

Observer	Blood Culture	Pneumonia	Duration, Weeks	Treatment	Organism Obtained from Local Lesion	History of Gonorrhea
Perry [10] (1928).....	Positive	3 times	15	15 transfusions; gonococcus vaccine	Yes; urethral smear	Yes
Williams [17] (1937).....	Negative	No	10	Kettering hypertherm; temperature to 108 F.	Yes; knee joint	Yes; 20 yr. before
Garlock: J. A. M. A. 97 : 999 (Oct. 3) 1931	Positive	No	12	Salpingectomy; 5 transfusions	Yes; cervical smear	No

obtained. There, however, seems to be little doubt of the diagnoses in the third case.

Certain essential features of these 3 cases and the treatment used are presented in table 4.

TREATMENT

The treatment and the important diagnostic points in the 3 cases of my series in which the patients recovered are given in table 5. The case of probable gonococcemia (case 23) seen recently at St. Luke's Hospital is not included in this table.

In summary, accepted forms of treatment would seem to be: (1) administration of sulfanilamide, up to 150 grains (9.72 Gm.) daily; (2) artificial fever induced by the Kettering hypertherm; (3) blanketing the patient, thus utilizing the patient's body heat to maintain a fever; (4) multiple blood transfusions, and (5) surgical removal of any focus of infection (frequently never found even at an autopsy).

That sulfanilamide must be given with great caution is illustrated by its effects in a case of subacute bacterial endocarditis recently at

TABLE 5.—*Data for Three Cases with Recovery in Present Series*

Case No.	Electrocardiogram	History of Gonorrhea	Gonococcus Isolated	Treatment	No. Weeks After Onset Before Diagnosis	Duration of Disease	No. of Positive Blood Cultures	No. of Negative Blood Cultures	History of Previous Heart Disease	Cardiac Involvement	Gonococcus Complement Fixation	Temperature
10	Elevated ST segment and diphasic P wave in leads I and II; normal after recovery	2 mo. before	Yes; urethral smear; patient had salpingitis and articular involvement	Kettering hypertherm	4	14 wk.	None	8	None	Systolic murmur at base and apex; loud pericardial friction rub	Positive; negative after recovery	Septic, to 107°; recovery following highest sustained temperature
14	No change	25 yr. before	No	Multiple transfusions in conjunction with the patient's high temperature	14	9 mo.	None	9	None	Systolic and diastolic murmurs at apex; systolic murmur at base varied from day to day; gallop rhythm	Positive	Septic to 106°; recovery following highest sustained temperature
20	No change	4 mo. before	Yes; from the blood	1 transfusion	14	18 wk.	3	1	None	Systolic murmur at apex; diastolic murmur at the base	Positive	Septic, to 105°; recovery following highest sustained temperature

St. Luke's Hospital. The patient was given from 80 to 200 grains (5.17 to 12.96 Gm.) daily for three weeks. His blood counts are given in table 6. The administration of the drug was stopped some time before the lowest count was obtained.

TABLE 6.—*Effect of Sulfanilamide on Blood Count*

Date	Hemoglobin, per Cent	Red Blood Cells	White Blood Cells	Neutrophils per Cent	Lymphocytes per Cent	Large Mononuclear Cells and Transition Forms, per Cent
3/17/38	80	5,160,000	25,500	88	9	3
4/ 7/38	50	3,100,000	11,700	80	16	4
4/ 9/38	53	3,500,000	11,200	89	10	1
4/11/38	52	3,850,000	4,600	52	18	..
4/13/38	45	3,100,000	800	4	96	..
4/15/38	60	3,300,000	700	2	98	..
4/17/38	50	3,250,000	350	..	100	..
4/18/38	51	3,400,000	200	..	100	..

CONCLUSIONS

Gonorrheal endocarditis is a fairly common disease. The diagnosis can and should be made early so that proper treatment may be instituted. Since a positive blood culture is frequently hard to obtain and is not the only diagnostic criterion, it is not absolutely necessary, and it may be dangerous to delay the diagnosis for lack of this one determination. The high percentage of diagnoses made at autopsy bears mute testimony to this. The high mortality should, in the future, be curtailed, and the majority of the patients should recover.

Dr. Edgar Mayer and Dr. Harry Keil read this paper and offered suggestions.

BACTERIAL ENDOCARDITIS AND SYPHILIS OF THE AORTIC VALVE

DAVID H. ROSENBERG, M.D.
CHICAGO

It has long been known that bacterial endocarditis usually develops on valves which have been the seat of a preexisting deformity. Particularly is this true of the subacute type of the disease. Moreover, it has been well recognized that in the vast majority of instances the antecedent defect arises as a sequel of rheumatic fever and that less commonly it is the result of a congenital malformation. Yet no specific reference pertaining to the coexistence of bacterial endocarditis and syphilitic involvement of the aortic valve appeared in the literature until 1917, when Libman [1] remarked on the infrequency with which subacute bacterial endocarditis attacks valves previously damaged by syphilis. He reiterated this observation in 1918,[2] in 1920 [3] and again in 1923,[4] pointing out in striking contrast the comparably high incidence of both rheumatic and syphilitic aortic valvular disease per se. Unfortunately, the number of such cases observed by Libman is not recorded in his papers. Since then numerous publications have appeared indicating the rarity of this combination, but, when subjected to critical analysis, only a few of the reported cases may be regarded as proved.

It is therefore appropriate at this time to present a critical review of the literature and to add 7 proved instances of syphilitic aortic valvular disease complicated by acute or subacute bacterial endocarditis, thus directing further attention to the coexistence of these lesions.

DIAGNOSTIC CRITERIA

That there may be no misinterpretation of what has been accepted as pathologic evidence of syphilitic valvular disease and of bacterial endo-

From the Department of Medicine and the Department of Pathology of the Michael Reese Hospital, the Department of Pathology of Cook County Hospital and the Department of Medicine, Northwestern University School of Medicine.

1. Libman, E.: Affections of the Valves of the Heart, M. Clin. North America **1**:573 (Nov.) 1917.

2. Libman, E.: Streptococcic and Influenzal Endocarditis, M. Clin. North America **2**:117 (July) 1918.

3. Libman, E.: Discussion on Clinical Significance and Course of Subacute Bacterial Endocarditis, Brit. M. J. **2**:304 (Aug. 28) 1920.

4. Libman, E.: Characterization of Various Forms of Endocarditis, J. A. M. A. **80**:813 (March 24) 1923.

carditis respectively, a few prefatory remarks seem apposite. In accord with the criteria of Cabot,[5] Karsner,[6] Saphir and Scott [7] and others, the following gross anatomic changes were regarded in this study as pathognomonic of syphilis of the aortic valve: (1) widening of the commissures separating the aortic leaflets, (2) fusion of the lateral portions of the cusps to the aortic wall of the sinus of Valsalva and (3) wrinkling and puckering of the aortic intima immediately above the aortic valve.

The anatomic differentiation between the acute and subacute forms of bacterial endocarditis is notably difficult in some instances. For the purpose of this study, however, the criteria laid down by Buchbinder and Saphir [8] for the diagnosis of subacute bacterial endocarditis were accepted as adequate. Those authors expressed the opinion that the presence of the majority of the following anatomic changes was in favor of this diagnosis: (1) large vegetations, (2) evidence of old valvular lesions (rheumatic, nonspecific, syphilitic or congenital malformations), (3) involvement of the adjacent mural, auricular and ventricular endocardium and chordae tendineae, (4) minute ulcerations of the leaflets of the valve and (5) presence of cocci in chains in sections of the vegetations. Clinically, conditions lasting for six weeks or longer were regarded as of the subacute type.

REVIEW OF THE LITERATURE

Kastner [9] (1918) recorded a single instance of a 32 year old woman with a history of "rheumatic" pains in the left hip for one and a half years. The clinical signs of endocarditis lenta, aortic insufficiency and tertiary syphilis were elicited. The blood culture revealed Streptococcus viridans, and the Wassermann reaction of the blood was positive. At necropsy, ulcerative endocarditis of the aortic valve, syphilitic aortitis and aortic insufficiency were observed. The aortic cusps were thickened and shortened, but no description of the commissures is included in the protocol. Although several subsequent authors have accepted this case as an undisputed instance of syphilitic aortic insufficiency, on the basis

5. Cabot, R. C.: Facts on the Heart, Philadelphia, W. B. Saunders Company, 1926.

6. Karsner, H. T.: The Pathology of Endocarditis: A Summary Review, J. A. M. A. **96**:411 (Feb. 7) 1931.

7. Saphir, O., and Scott, R. W.: The Involvement of the Aortic Valve in Syphilitic Aortitis, Am. J. Path. **3**:527 (Sept.) 1927. Scott, R. W., and Saphir, O.: The Pathogenesis of Syphilitic Aortic Insufficiency, Tr. A. Am. Physicians **42**:36, 1927.

8. Buchbinder, W. C., and Saphir, O.: Heart Failure in Subacute Bacterial Endocarditis, Arch. Int. Med. **64**:336 (Aug.) 1939.

9. Kastner, A.: Ueber Endocarditis lenta, Deutsches Arch. f. klin. Med. **126**:370 (June) 1918.

of the criteria set forth in the preceding section the syphilitic nature of the valvular deformity cannot be regarded as proved.

Briggs [10] (1922) reviewed the literature and added a proved instance of acute verrucous endocarditis of the aortic and the mitral valve with typical syphilitic aortic insufficiency (separation of the aortic commissures) and syphilitic aortitis, which had followed a subacute course. Blood cultures disclosed nonhemolytic streptococci, and the Wassermann reaction of the blood was positive.

Curschmann [11] (1922) observed a clinical instance of "endocarditis lenta" and aortic insufficiency, in which the Wassermann reaction of the blood was positive. The blood culture revealed a streptococcus similar in characteristics to the pneumococcus. However, since the patient related a remote history of recurrent acute rheumatic fever, one cannot regard this case as proved without anatomic confirmation.

Blumer [12] (1923) found only 1 instance among records of 330 collected cases of subacute bacterial endocarditis in which "an old valve lesion" and a history of syphilis were mentioned. No further details concerning this case are given, but the appended bibliography indicates that it is likely that it is the one described by Kastner.[9]

In a study of 35 cases of streptococcic aortic endocarditis, Thayer [13] (1926) observed 2 cases of syphilitic aortitis, but there was "little evidence to suggest syphilitic disease of the aortic valve in any case." In his group of cases of acute bacterial endocarditis due to Staphylococcus albus, in only 1 instance was the disease superimposed on a preexisting syphilitic aortic insufficiency with accompanying syphilitic aortitis.

Pineles [14] (1926) recorded 4 cases in which there was clinical evidence of syphilitic aortitis and aortic insufficiency and in which signs of subacute bacterial endocarditis subsequently developed. In only 1 instance (case 4) was an autopsy performed, revealing verrucous endocarditis of the aortic valve and syphilitic aortitis with encroachment on the aortic leaflets; the blood culture was negative, and the Wassermann reaction of the blood weakly positive. Although there is strong evidence favoring the clinical diagnosis of syphilitic aortic insufficiency in the remaining 3 cases, its coexistence with bacterial endocarditis cannot be accepted as proved without necropsy.

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10. Briggs, L. H.: Bacterial Endocarditis as a Sequel to Syphilitic Valve Defect, Am. J. M. Sc. **164**:275 (Aug.) 1922.

11. Curschmann, H.: Ueber Endocarditis chronica (lenta), München. med. Wchnschr. **69**:419 (March 24) 1922.

12. Blumer, G.: Subacute Bacterial Endocarditis, Medicine **2**:105, 1923.

13. Thayer, W. S.: Studies on Bacterial (Infective) Endocarditis, Johns Hopkins Hosp. Rep. **22**:1, 1926.

14. Pineles, F.: Aortenlues und Endocarditis lenta, Med. Klin. **22**:444 (March 19) 1926.

Cade [15] (1927) observed an instance of syphilitic aortitis associated with vegetative aortic and mitral endocarditis. The aortic cusps were indurated, retracted and insufficient, but without a description of the commissures the presence of syphilitic changes in the aortic valve remains in doubt.

Sumbal [16] (1928) reported 18 instances in which the conditions were diagnosed clinically as syphilis associated with subacute bacterial endocarditis. In 10 of these, postmortem examinations were made: In 5 the underlying valvular deformity was either typically rheumatic or very probably rheumatic, according to the protocols; for the remaining 5 no anatomic description of the aortic valves is recorded beyond that of the vegetations; in only 1 was syphilitic aortitis observed, and in this instance the aortic valve is not described. Skursky [17] (1929) cited 2 cases of malignant endocarditis of the aortic valve associated with syphilitic aortitis (necropsy). Again, the protocols offer no comment concerning the possibility of syphilitic involvement of the aortic valve or about the state of the aortic commissures.

Schnabel and Leivy [18] (1931) recorded a proved instance of acute bacterial endocarditis superimposed on a syphilitic deformity of the aortic valve. The Wassermann reaction of the blood was strongly positive, and clinical and anatomic evidence of tabes dorsalis was found. Blood cultures were negative. Lemann [19] (1931) observed an instance of subacute bacterial (pneumococcic) endocarditis with aortic insufficiency in a patient with a history of syphilis. The Wassermann reaction of the blood was strongly positive, and clinical signs of neurosyphilis were elicited. Only the following brief anatomic description of the heart is given: "The valves on the left side presented large cauliflower-like growths." There are no remarks concerning the aorta. Although Lemann submitted that ". . . we are probably justified in assuming that this aortic regurgitation had been produced by the syphilitic process," it is apparent that the anatomic evidence, according to the record, is distinctly lacking. A chronologic review of the clinical history shows that manifestations of bacterial endocarditis were already

15. Cade, M. A.: Endocardite infectieuse à marche lente greffée sur une aortite syphilitique, Lyon méd. **139**:731 (June 19) 1927.

16. Sumbal, J.: Case of Endocarditis Due to Untreated Syphilitic Infection, Bratisl. lekár. listy **8**:267 (May); 281 (June) 1928.

17. Skursky, J.: Über Fälle maligner Endokarditis bei Aortenlues, Wein. klin. Wchnschr. **42**:293 (March 7) 1929.

18. Schnabel, T. G., and Leivy, F. E.: Tabes Dorsalis, Syphilitic Aortitis, Aortic Regurgitation, and Bacterial Endocarditis, M. Clin. North America **15**:325 (Sept.) 1931.

19. Lemann, I. I.: Subacute Bacterial Endocarditis (Pneumococcal) Engrafted upon Preëxisting Syphilitic Valvular Disease, Internat. Clin. **2**:66 (June) 1931.

present when aortic regurgitation was first noted, and therefore they can offer no assistance in determining the onset of the latter.

Fulton and Levine [20] (1932) analyzed 111 clinical cases of subacute bacterial endocarditis, and noted but 1 instance which might be regarded as illustrative of this combination. They concluded that "syphilis as a predisposing agent in streptococcus endocarditis is extremely rare." Craven [21] (1932) reviewed the literature and added a proved instance of syphilitic aortitis and aortic insufficiency complicated by aortic endocarditis due to Str. viridans.

Brahic, Recordier and Sarradon [22] (1934) reported in abstract the case of a 45 year old patient who had manifested signs of syphilitic aortic insufficiency and later showed evidence of subacute bacterial endocarditis. Blood cultures were repeatedly negative. At necropsy, vegetative aortic endocarditis was observed, but no further description of the heart and aorta is recorded. Although the title of the abstract offers confirmation, further data are necessary before this case can be accepted as proved.

Perry [23] (1936) commented on the rarity of this combination and presented photographic evidence of subacute bacterial endocarditis engrafted on a typical syphilitic valvular deformity, the separation of the commissures being clearly demonstrable. Smith [24] (1937) and McMillan and Wilbur [25] (1937) added single proved instances, and Martin and Adams [26] (1938) reported 2 proved cases (cases 1 and 4) of bacterial endocarditis engrafted on typical syphilitic aortic valves. Of Martin and Adams' remaining 3 cases, 2 were of syphilitic aortitis with recent vegetative aortitis, but the aortic leaflets were normal. The fifth case was an instance of acute vegetative endocarditis (Str. viridans and Escherichia coli) of the mitral cusp of the aortic valve, with aortic insufficiency and syphilitic aortitis, but no comment on the aortic commissures is included in the protocol.

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20. Fulton, M. N., and Levine, S. A.: Subacute Bacterial Endocarditis, with Special Reference to the Valvular Lesions and Previous History, Am. J. M. Sc. **183**:60 (Jan.) 1932.

21. Craven, E. B., Jr.: Syphilitic Aortic Endocarditis and Superimposed Bacterial (Streptococcus Viridans) Endocarditis, Am. J. Path. **8**:81 (Jan.) 1932.

22. Brahic, J.; Recordier, M., and Sarradon, P.: Endocardite lente greffée sur une sigmoïdite aortique spécifique, Marseille méd. **1**:766 (June 15) 1934.

23. Perry, C. B.: Bacterial Endocarditis, Bristol, England, John Wright & Sons, Ltd., 1936.

24. Smith, F. J.: The Coexistence of Syphilis of the Aorta and Bacterial Endocarditis: A Report of Three Cases, Internat. Clin. **2**:1 (June) 1937.

25. McMillan, R. L., and Wilbur, E. L.: Staphylococcic Endocarditis Superimposed on Syphilitic Aortic Endocarditis, J. A. M. A. **109**:1194 (Oct. 9) 1937.

26. Martin, H. E., and Adams, W. L., Jr.: Bacterial Endocarditis Superimposed on Syphilitic Aortitis and Valvulitis: A Clinicopathological Study with Five Case Reports, Am. Heart J. **16**:714 (Dec.) 1938.

Gallavardin and Gravier [27] (1927), Raybaud, Jouve and Farnarier [28] (1935) and Areta [29] (1935) observed single instances of subacute bacterial endocarditis associated with syphilitic aortitis, but in none was there evidence of syphilitic valvular disease. Another case recorded by François and Jouve [30] (1934) revealed neither conclusive evidence of syphilitic aortitis nor anatomic signs of syphilis of the aortic valve.

Musser [31] (1933), Keefer [32] (1937), White [33] (1937) and Hamman and Brown [34] (1937) are but an added few of the recent authors who have remarked on the rarity with which subacute bacterial endocarditis involves syphilitic aortic valvular lesions. Curiously, such authoritative textbooks on pathology as that of Boyd [35] (1935) and that of Muir [36] (1936) do not mention syphilis as a predisposing factor; nor does Stokes [37] in his book "Modern Clinical Syphilology."

Thus, in summary (table 1), it may be said that since Libman's original observation of the infrequent association of subacute bacterial endocarditis with syphilitic aortic valvular disease, only 7 proved instances of such a condition have appeared in the literature. In 3 others, the complicating endocarditis was of the acute form, making a total of 10 proved cases of bacterial endocarditis engrafted on syphilitic valves. In 4 more, in view of the incomplete descriptions in the protocols, the

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27. Gallavardin, L., and Gravier, L.: Endocardite infectieuse greffée sur aortite spécifique, Lyon méd. **139**:727 (June 19) 1927.

28. Raybaud, A.; Jouve, A., and Farnarier, G.: Maladie de Jaccoud-Osler greffée sur une aortite chronique syphilitique, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:136 (Feb. 4) 1935. Raybaud, A., and Jouve, A.: Endocardite maligne lenta (maladie de Jaccoud-Osler) et lésions aortiques syphilitiques, J. de méd. et chir. prat. **106**:282 (April) 1935.

29. Areta, T.: Endocarditis lenta maligna con aneurisma de la radial, Semana méd. **2**:645 (Aug. 29) 1935.

30. François, L., and Jouve, A.: Endocarditis maligne greffée sur une aortite syphilitique, Marseille méd. **2**:726 (Dec. 15) 1934.

31. Musser, J. H.: Subacute Bacterial Endocarditis, Ann. Int. Med. **7**:715 (Dec.) 1933.

32. Keefer, C. S.: Subacute Bacterial Endocarditis: Active Cases Without Bacteremia, Ann. Int. Med. **11**:714 (Nov.) 1937.

33. White, P. D.: Heart Disease, ed. 2, New York, The Macmillan Company, 1937, p. 257.

34. Hamman, L., and Brown, T. M.: Subacute Bacterial Endocarditis, Internat. Clin. **3**:33 (Sept.) 1937.

35. Boyd, W.: The Pathology of Internal Diseases, ed. 2, Philadelphia, Lea & Febiger, 1935, p. 33.

36. Muir, R.: Text-Book of Pathology, ed. 4, Baltimore, William Wood & Company, 1936.

37. Stokes, J. H.: Modern Clinical Syphilology, ed. 2, Philadelphia, W. B. Saunders Company, 1934, pp. 539 and 1053.

coexistence of syphilitic valvular deformities must be regarded as doubtful, and in 29, the presence of syphilitic disease of the aortic valve remains unproved (tables 2 and 3).

TABLE 1.—*Proved Cases of Bacterial Endocarditis Superimposed on Syphilitic Aortic Valvular Disease*

Author	Age	Sex	Acute Type	Subacute Type	Organism
Briggs	35	M	..	1	Nonhemolytic streptococcus
Thayer	..	..	1	..	Staph. albus
Pineles	54	M	..	1	
Schnabel and Leivy	50	F	1	..	
Craven	23	M	..	1	Str. viridans
Perry	..	..	..	1	Not stated
Smith	63	M	1	..	Staph. albus
McMillan and Wilbur	47	M	..	1	Staph. haemolyticus aureus
Martin and Adams	60	M	..	1	Str. viridans
	28	M	..	1	Str. viridans
			3	7	

TABLE 2.—*Doubtful Cases of Bacterial Endocarditis Superimposed on Syphilitic Aortic Valvular Disease*

Author	Age	Sex	Acute Type	Subacute Type	Organism
Kastner	32	F	..	1	Str. viridans
Cade	42	M	..	1	Not stated
Brahic, Recordier and Sarradon	45	M	..	1	
Martin and Adams	42	M	1	..	Str. viridans and E. coli
			1	3	

TABLE 3.—*Unproved Cases of Bacterial Endocarditis and Syphilitic Aortic Valvular Disease*

Author	Acute Type	Subacute Type	Organism	Comment
Curschmann	..	1	Streptococcus	No autopsy
Pineles	..	1	Str. viridans	No autopsy
		2	.....	No autopsies
Gallavardin and Gravier	..	1	Not stated	Syphilitic aortitis alone
Sumbal	..	18	Not stated	Autopsies in 10; syphilitic aortitis in only 1 of the 10 (uncomplicated)
Skursky	..	1	.....	No reference to syphilitic disease of aortic valve
		1	Not stated	
Lemann	..	1	Pneumococcus	Anatomic description inconclusive
François and Jouve	..	1	.....	Inconclusive anatomic evidence of syphilis
Raybaud, Jouve and Farnarier	..	1	Streptoenterococcus	Syphilitic aortitis without extension to valve
Areta	..	1	.....	Syphilitic aortitis without extension to valve
		29		

MATERIAL

In close accordance with the aforementioned diagnostic criteria, the case reports to be presented were culled from the clinical and necropsy material available at the Michael Reese and the Cook County Hospital and from my own clinical

case records. Only those cases were selected in which the pathologic diagnosis of syphilitic disease of the aortic valve was unequivocal.

Of 45 cases of bacterial endocarditis (1, acute; 44, subacute) among a total of 3,143 cases in which necropsy was performed at the Michael Reese Hospital during the ten year period from 1929 to 1938, in 2 (1, acute; 1, subacute) the disease was engrafted on a preexisting syphilitic aortic insufficiency; in 1 it had developed on a congenital bicuspid aortic valve damaged by syphilis, and in 1 there was syphilitic aortitis alone. At the Cook County Hospital during the same ten year period, 228 cases of bacterial endocarditis (31, acute; 197, subacute) were observed among a total of 11,666 cases in which necropsy was done. Of these, in 5 (1, acute; 4, subacute) the disease had developed on syphilitic aortic valves. In 10 others it was associated with syphilitic aortitis, but the aortic valves were either normal or affected by disease other than syphilis.

REPORT OF CASES

CASE 1.—J. R., a white man aged 60, was seen on April 13, 1936, because of cough, expectoration, dyspnea and weakness. He had been in excellent health until one and a half years before, when progressive weakness and dyspnea became apparent. He had been coughing frequently for four months, expectorating large amounts of colorless mucus. On March 6 a transient, sudden and severe backache in the left part of the lumbar region developed. Recently, sudden pain appeared in the left foot, radiated to the thigh and lasted three days. He had lost 4 pounds (1.8 Kg.) in four months.

Past History.—In December 1935 a tooth was extracted because of a periapical abscess. No history of rheumatic fever, chorea or syphilis could be elicited. With the exception of the dental infection, the history was noncontributory.

Physical Examination.—Examination on admission revealed a well developed, well nourished man, who appeared dyspneic and slightly pale. The temperature was 100 F. (oral); the respiratory rate was 28, and the pulse rate, 92 per minute. The pupils were slightly irregular, but reacted well to light and in accommodation. Examination of the heart disclosed an apical impulse, visible, heaving and localized in the fifth interspace in the midclavicular line. The right border was 6 cm. from the midsternal line in the fourth interspace, and the left border was 11 cm. to the left in the fifth interspace. A loud blowing systolic murmur was audible over the entire precordium, most intense at the apex and in the aortic area. A prolonged blowing diastolic murmur was heard at the third left interspace near the sternal border and was transmitted to the right first interspace, over the sternum, to the apex. The aortic second sound was accentuated and louder than the pulmonic second sound. There was a Corrigan pulse, as well as a capillary pulse and a positive Duroziez's sign. The radial arteries were thickened, and the brachial arteries were tortuous and pulsating. Examination of the lungs revealed impaired resonance at the bases posteriorly, with many subcrepitant rales; there was hyperresonance elsewhere. The liver edge was palpated 8 cm. below the costal margin on inspiration, and was sharp, smooth and tender. The spleen was palpable on inspiration, and the edge was rounded. There was slight pretibial edema. The patellar reflexes were hyperactive, and no achilles tendon reflexes were elicited. The fingers were hippocratic. The rest of the examination gave negative results. The blood pressure was 145 systolic and 50 diastolic.

Laboratory Examination.—The urine had a specific gravity of 1.018 with an albumin content of 1 plus and no sugar; microscopic examination of the urine

showed 2 to 10 erythrocytes per high power field. Analysis of the blood revealed a hemoglobin value of 70 per cent (Sahli); erythrocytes, 4,000,000 per cubic millimeter, and leukocytes, 11,200, with a normal differential count. The Wassermann reaction of the blood was 1 plus, and the Kahn reaction, 4 plus. A culture of the blood revealed Str. viridans. A teleoroentgenogram showed the cardiothoracic ratio to be 18.0/29.0 cm., the contour of the left side of the heart normal and the right border far beyond normal limits. The blood culture and the Wassermann and Kahn tests were repeated on April 20, with identical results. At this time it was learned that the patient had received antisyphilitic treatment in the past.

Course.—Recurrent showers of petechiae appeared on the abdomen, extremities, eyelids, thorax and back. Pain in the left upper quadrant associated with splenic swelling and tenderness and a rise in temperature occurred at infrequent intervals and subsided in four to five days. On May 1 there was transitory diplopia. The apical systolic murmur became louder and rough, and a diagnosis of vegetative endocarditis of the mitral valve was made. The general course of the illness was progressively downhill. One week before death, examination of the blood disclosed: hemoglobin, 50 per cent; erythrocytes, 2,700,000 per cubic millimeter, and leukocytes, 12,000. The fever was intermittent, with afebrile periods of one to two days; the average temperature was from 99 to 100 F. (oral), and occasionally it was 103.4 F. Death occurred on November 6, following bilateral bronchopneumonia. The diagnosis was as follows: subacute bacterial endocarditis (aortic and mitral), syphilitic aortic insufficiency, syphilitic aortitis and neurosyphilis.

Autopsy (performed by Dr. M. Lev).—Gross Examination: The heart weighed 550 Gm. The mitral leaflets presented numerous semifriable vegetations. The aortic cusps were moderately thickened, and their edges were rolled. There was a moderate separation of all three commissures. The right anterior cusp was covered by a mass of small vegetations extending over the upper portion of the muscular ventricular septum and over the anterior portion of the pars membranacea. Small groups of vegetations were observed on the left anterior, and a few on the posterior, aortic cusp. The mouth of the right coronary artery was restricted by grayish blue puckered plaques. The aorta was covered by a conglomeration of plaques, and the intima was wrinkled and puckered (figs. 1 and 2).

Microscopic Examination: The cusp of the aortic valve was denuded from the epithelium and was covered by clumps of fibrin which showed small cocci arranged in chains. The edges of the cusp revealed smaller and larger areas of necrosis. The cusp itself showed a number of spindle-shaped cells arranged in the form of bands, as well as lymphocytes and endothelial leukocytes. Close to the base of the cusp, there were areas of hyalinization and several blood vessels surrounded by lymphocytes. Examination of the aorta revealed in the adventitia a new formation of connective tissue, with hyalinization of many of the connective tissue fibers. Some of the vasa vasorum showed marked intimal proliferation. There was an extensive infiltration of lymphocytes in the perivascular spaces. The media revealed interruptions in the course of the elastic fibers as well as connective tissue replacement and a number of small blood vessels, surrounded by lymphocytes. The intima contained areas of fibrosis, hyalinization and calcification.

The pathologic diagnosis was as follows: syphilitic aortitis, syphilitic aortic insufficiency, restriction of the mouth of the right coronary artery and subacute bacterial endocarditis of the aortic and the mitral valve.

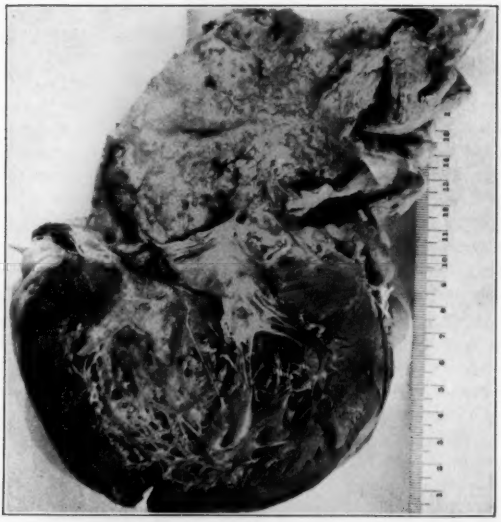

Fig. 1.—Heart and aorta, showing syphilitic aortitis and aortic insufficiency as well as subacute bacterial endocarditis of the aortic and the mitral valve.

Fig. 2.—Heart and base of the aorta under higher magnification, showing wrinkling and puckering of the aortic intima, restriction of the mouth of the right coronary artery, separation of the aortic commissures, vegetations (especially on the aortic cusps) and ulceration of an aortic and a mitral leaflet.

CASE 2.—J. J., a white man aged 56, was admitted to the Michael Reese Hospital on Oct. 7, 1938, complaining of choking spells and constipation. In 1931 progressive weakness, swelling of the legs and dyspnea on exertion set in. A "leaking aortic valve" was observed at this time. Rest and reduction in weight effected considerable improvement. In the last three years the dyspnea had grown worse, and increasing weakness and swelling of the ankles and feet recurred. Three weeks before admission generalized aching and cough appeared. The dorsum of the left foot became reddened, tense and shiny but improved within five days. The dyspnea, weakness and orthopnea were decidedly worse thereafter, and paroxysmal nocturnal dyspnea developed. The patient had been markedly constipated for three weeks, had had no appetite and had vomited on two occasions. He had lost 20 pounds (9 Kg.) in two years.

Past History.—The patient had gonorrhea and a chancroid at the age of 20 years. In 1930 his wrists became painful and swollen (?), and there was generalized muscular pain lasting three days. The past history otherwise was without significance.

Physical Examination.—On admission the patient appeared fairly well nourished, well developed, slightly dyspneic and orthopneic. The temperature was 99.8 (rectal); the pulse rate was 98, and the respiratory rate 22, per minute. The skin and mucous membranes were pale. The tonsils were enlarged. There were marked arterial and venous pulsations in the neck. The lungs were normal except for occasional subcrepitant rales at the bases posteriorly. The apical impulse was palpable and visible in the fifth interspace just outside the midclavicular line. The cardiac dulness was slightly increased to the right and moderately to the left. Blowing systolic and diastolic murmurs were audible at the apex and right base, and a blowing systolic murmur was heard over the pulmonic area. There was a Corrigan pulse. The liver was palpated 10 cm. below the costal margin and was sharp and tender. The spleen was 4 cm. below the costal margin. Clubbing of the fingers and edema of the sacrum, legs and feet were observed. The blood pressure was 146 systolic and 42 diastolic.

Laboratory Examination.—The value for hemoglobin was 75 per cent, for erythrocytes 3,550,000 per cubic millimeter and for leukocytes 14,300, with a differential count of 77 per cent polymorphonuclears, 15 per cent lymphocytes, 2 per cent myelocytes, 5 per cent immature leukocytes and 1 per cent metamyelocytes. Polychromatophilia was present. Wassermann and Kahn tests gave readings of 4 plus. The urine had a specific gravity of 1.016 and an acid reaction. There was a 2 plus reaction for albumin. Occasional leukocytes and erythrocytes and a few hyaline casts were observed. The nonprotein nitrogen value was 76 mg. per hundred cubic centimeters. A teleoroentgenogram showed an increased cardiothoracic ratio of 19.5/32.6 cm., a prominent ventricular bow, a straightened left border and a wide aortic diameter. A blood culture was negative.

Course.—The temperature varied from 99.6 to 102 F. (rectal). The pulse rate was 80 to 100 per minute. Dyspnea and restlessness were prominent. Death occurred suddenly on October 12. The diagnosis was as follows: subacute bacterial endocarditis (?), syphilitic aortitis and aortic insufficiency, myocardial hypertrophy and dilatation and advanced congestive heart failure.

Autopsy (performed by Dr. M. Lev).—Gross Examination: The heart weighed 575 Gm. The aortic cusps were moderately thickened and retracted, with distinct separation of the commissures. On the left anterior cusp there was a grayish yellow, adherent vegetation about 1.2 cm. in length. A smaller similar vegetation was

observed on the posterior cusp. The aortic leaflet of the mitral valve presented many large, confluent, grayish yellow, adherent vegetations. The ostium of the left coronary artery was distinctly narrowed. The ascending limb of the aorta was moderately dilated. The lining exhibited multiple bluish gray, longitudinally wrinkled plaques, most marked at, and just above, the aortic valve.

Microscopic Examination: The vegetations presented a mass of polymorphonuclear leukocytes lying in a homogeneous material which stained pink. The aorta showed many mononuclear cells infiltrating the media and surrounding the vasa vasorum in the adventitia. The intima was thickened and hyalinized.

The pathologic diagnosis was: syphilitic aortitis with aneurysmal dilatation of the ascending part of the aorta and narrowing of the left coronary ostium, syphilitic aortic insufficiency and acute vegetative endocarditis of the aortic and the mitral valve.

CASE 3.—J. H., a Negro aged 45, was admitted to the Cook County Hospital on Feb. 14, 1930, complaining of frontal headache, throbbing pains in the head and dizziness of two and a half months' duration. He had also noted palpitation and slight dyspnea on exertion for several months. Three days before admission "everything went black" before his eyes, and the left upper extremity became paralyzed, although consciousness was retained.

Past History.—Except for a penile sore thirty years ago the previous history was noncontributory.

Physical Examination.—The patient was well developed and well nourished. He was unable to move the left upper extremity. The temperature was 99.8 F. (oral); the pulse rate was 100, and the respiratory rate 24, per minute. The pupils reacted sluggishly to light but well in accommodation. The left nasolabial fold was smooth; there was drooping of the left angle of the mouth. The teeth were carious. There were marked arterial pulsations in the neck. Examination of the heart showed the apical impulse to be visible, forceful and palpable in the sixth interspace. The left border was 12 cm. from the midsternal line in the sixth interspace, and the right border was 4 cm. to the right in the fourth interspace. There were blowing systolic and diastolic murmurs over the entire precordium, loudest over the aortic area. Corrigan pulse and capillary pulse were observed, and Duroziez's sign was present. The left upper extremity was flaccid. Patellar and achilles tendon reflexes were absent; the Babinski reflex was normal, and the left cremasteric reflex was absent. The rest of the examination gave negative results. The blood pressure was 150 systolic and 90 diastolic.

Laboratory Examination.—The urine was normal. The Wassermann reaction of the blood was negative. Tests of the spinal fluid revealed no abnormalities. Clinical analysis of the blood showed a hemoglobin value of 45 per cent; an erythrocyte count of 2,500,000 per cubic millimeter and a leukocyte count of 16,500. A teleoroentgenogram showed marked prominence of the aortic arch. Blood cultures taken on April 30, May 12 and May 26 yielded a moderately long chain streptococcus with a definite capsule. It could not be identified by subculture, but was neither Str. viridans nor Str. haemolyticus.

Course.—Weakness, pain in the left hypochondrium and swelling of the feet developed. Nocturia occurred. Petechiae appeared. The spleen became palpable. The temperature averaged 100 to 101 F. (oral), with a maximum of 103 F. The pulse rate ranged from 90 to 110 per minute. The course was progressively downhill, terminating in stupor and death on July 20. The diagnosis was: subacute bacterial endocarditis, syphilitic aortitis and aortic insufficiency.

Autopsy (performed by Dr. R. H. Jaffé).—Gross Examination: The heart weighed 600 Gm. On the anterior cusp of the mitral valve there were two soft, adherent, polypoid, yellow-gray deposits measuring 5 by 3 mm. In the middle of the cusps there was an irregular hole 3 by 2 mm. in diameter, and at the lower edge were soft, pink-gray, polypoid deposits 7 by 5 by 1.5 mm. Above the hole a thin-walled, yellowish pink outpouching was observed. The aortic cusps were slightly thickened and showed separation of the commissures as well as synechiae between the commissures and the wall of the aorta. The right cusp showed a large, soft, yellow-gray deposit 2.2 by 0.8 by 0.7 cm. Granular and nodular deposits of similar material extended over the ventricular aspect of the posterior leaflet. Examination of the aorta revealed extensive wrinkling of the intima throughout the ascending portion and the arch.

Microscopic Examination: The aorta showed numerous flame-shaped scars throughout the media, with adjacent areas of diffuse necrosis. Cellular granulation tissue penetrated the media.

The pathologic diagnosis was: thromboendocarditis of the aortic and the mitral valve, syphilitic aortic insufficiency and aortitis.

CASE 4.—W. M., a white man, aged 36, was admitted to the Cook County Hospital on Feb. 7, 1933, complaining of shortness of breath and pain in the chest and neck. Five weeks before, dyspnea was noted on exertion. Shortly thereafter, pallor of the skin, aching pain behind the sternum and along the sides of the neck, dull epigastric pain, palpitation and decreasing appetite appeared. These symptoms temporarily improved when the patient rested in bed, but became progressively worse when he resumed work. A dry cough and orthopnea developed, and, together with the other symptoms, persisted to the time of admission.

Past History.—The previous history was irrelevant except for probable rheumatic fever at the age of 6 years, but the details of this illness were obscure. No history of syphilis could be elicited.

Physical Examination.—The man was pale and dyspneic and appeared critically ill. The lips and nail beds were slightly cyanotic. The temperature was 96.6 F. (oral); the pulse rate was 96, and the respiratory rate 24 per minute. The conjunctivas and the buccal mucosa were pale. The mouth was edentulous. The submaxillary nodes were slightly enlarged. There were vigorous arterial pulsations in the neck. Dulness with subcrepitant rales was observed at the bases of the lungs posteriorly. The heart was enlarged, with a diffuse apical impulse in the left anterior axillary line in the sixth interspace. The right border was 5 cm. from the midsternal line in the fourth interspace. Blowing systolic and diastolic murmurs were heard over the entire precordium, the latter being loudest at the left third interspace. Corrigan pulse, capillary pulse and Duroziez's sign were elicited. The abdomen was moderately distended with fluid. The liver was palpated 12 cm. below the costal margin and was tender. The spleen was felt 4 cm. below the costal margin. Pretibial and sacral edema were observed. The blood pressure was 150 systolic and 80 diastolic.

Laboratory Examination.—The urine contained albumin (3 plus) and no sugar. Microscopic study of the urine revealed occasional erythrocytes, leukocytes and epithelial cells. Analysis of the blood showed a hemoglobin value of 78 per cent (Sahli), an erythrocyte count of 4,470,000 per cubic millimeter and a leukocyte count of 29,000, with a differential count of 80 per cent polymorphonuclears, 2 per cent myelocytes, 4 per cent metamyelocytes, 7 per cent small lympocytes and 7 per cent monocytes. Culture of the blood showed no growth.

Course.—Death occurred the following day. The maximum temperature was 100.6 F. (rectal).

Autopsy (performed by Dr. V. Levine).—Gross Examination: The heart weighed 660 Gm. The aortic valve showed a moderate separation of the commissures between the posterior and the right leaflet and the posterior and the left leaflet. There were fenestrations at the attachment of the left and posterior leaflet. The commissure between the right and the left aortic cusp was missing, and there was a gap 4 cm. in diameter between them. A purple-gray vegetation 0.5 by 1.0 by 0.1 mm. was attached to the left cusp. The right leaflet was thickened (3 mm.) and covered with gray nodules of pinhead size. The aorta showed marked scarring and wrinkling extending to the commissures.

Microscopic Examination: The aortic cusps showed cellular and vascular tissue rich in fibrocytes, small round cells and histiocytes and having an occasional neutrophilic leukocyte. The subendothelial layer was thickened and the uppermost layer presented, in places, fibrinoid necrosis. Examination of the aorta showed the adventitia to be thickened and hyalinized and to have a marked perivascular infiltration of lymphocytes with an occasional plasma cell and histiocyte. The media was thickened; newly formed capillaries extended to the intima and presented a decided perivascular infiltration of plasma cells, histiocytes and a few lymphocytes. Cultures of the spleen showed no abnormalities. The Kahn test of the blood taken post mortem gave a negative reading. The Wassermann test was anticomplementary. The pathologic diagnosis was: syphilitic aortic insufficiency, syphilitic aortitis and verrucous endocarditis of the aortic valve.

Case 5.—M. J., a Negress aged 45, was admitted to the Cook County Hospital on Jan. 20, 1934, complaining of fever and loss of weight. For three months she had been restless, tremulous and easily upset. She had felt feverish in the evenings and had been losing weight steadily. Nocturia was present, and she had been having pain in the left posterior portion of the lumbar region, radiating to the left hypochondrium.

Past History.—Except that the first pregnancy terminated in a miscarriage, the past history was irrelevant. The patient stated that she had never had a venereal disease.

Physical Examination.—The patient appeared fairly well nourished, well developed and not acutely ill. The temperature was 98.8 F. (oral); the pulse rate was 100, and the respiratory rate 20, per minute. The pupils were miotic and equal; they reacted sluggishly to light but well in accommodation. The conjunctivas and the buccal mucosa were pale. Examination of the lungs revealed impaired resonance and diminished tactile fremitus as well as suppressed breath sounds and subcrepitant rales at the right base posteriorly. The heart was slightly enlarged, with the left border at the nipple line. A soft blowing systolic murmur was heard at the right base, and a blowing diastolic murmur at the third left interspace near the sternum was transmitted to the right and downward. The aortic second sound was accentuated. Pain on pressure was elicited in the left hypochondrium. The fingers were slightly hippocratic. The patellar and achilles tendon reflexes were sluggish. The rest of the examination gave negative results. The blood pressure was 90 systolic and 40 diastolic.

Laboratory Examination.—The urine contained albumin (1 plus) and no sugar; microscopically, hyaline and many granular casts were observed. The hemoglobin value of the blood was 55 per cent, and the leukocytes numbered 8,700 per cubic millimeter, with a differential count of 56 per cent polymorphonuclears, 38

per cent small lymphocytes, 2 per cent basophils and 4 per cent monocytes. The Kahn reaction was 4 plus. Culture of the blood yielded Str. viridans. A teleoroentgenogram showed moderate cardiac enlargement with passive congestion at the bases of the lungs.

Course.—The clinical course was progressively downhill. A low grade remittent fever, averaging 100 to 102 F. (oral), was present daily. Death occurred on March 12. The diagnosis was: syphilitic aortitis, syphilitic aortic insufficiency with engrafted subacute bacterial endocarditis and neurosyphilis.

Autopsy (performed by Dr. R. H. Jaffé).—The heart weighed 300 Gm. The commissures of the aortic leaflets were separated for a distance of about 6 mm. The right and the left leaflets near the commissures were thickened and nodular. On the right leaflet there was a soft, adherent, purple-gray mass, 10 by 11 by 6 mm. The aortic surface of the other leaflets was covered by purple-gray, granular deposits measuring up to 4 by 2 by 1 mm. The aorta showed an irregular wrinkling and puckering of the intima, extending to the upper third of the descending thoracic aorta.

The pathologic diagnosis was: malignant endocarditis of the aortic valve, syphilitic aortic insufficiency and syphilitic aortitis.

Case 6.—M. L., a Negress aged 42, was admitted to the Cook County Hospital on March 8, 1934, complaining of pains over the body, weakness and fever. Four months before admission she had noted soreness in the bones and swelling and pain over the dorsum of the left hand with limitation of motion. Shortly thereafter, pain appeared in the knees and ankles. She had had fever for several weeks and had become progressively weaker. Knifelike pains above the right hip and shooting pains in the head had been present for seven to ten days.

Past History.—In 1925 the patient was bedridden for a short period, suffering from painful knees and ankles and swollen eyelids. At that time her physician informed her of a "leak" in her heart and of the presence of anemia, but she improved and had been well since then.

Physical Examination.—The patient was fairly well nourished and slightly dyspneic. The temperature was 100.6 F. (oral); the pulse rate was 120, and the respiratory rate 28, per minute. The pupils were contracted and slightly irregular and did not react to light; the scleras were hyperemic. The tonsils were enlarged. The cervical vessels pulsated visibly. The lungs were normal except for subcrepitant rales at the bases posteriorly. Examination of the heart revealed a diffuse precordial pulsation; the apex was just beyond the midclavicular line. The cardiac dulness was slightly increased to the left. Blowing systolic and diastolic murmurs were heard over the entire precordium, loudest at the base. Corrigan pulse, capillary pulse and Duroziez's sign were observed. The liver was palpated 4 cm. below the costal margin in the nipple line on inspiration and was sharp and tender. The spleen was felt 2 cm. below the costal margin on inspiration; the edge was rounded and of increased consistency. Patellar reflexes were absent. The rest of the examination gave normal results. The blood pressure was 178 systolic and 48 diastolic.

Laboratory Examination.—The hemoglobin of the blood was 55 per cent; the erythrocyte count was 3,000,000 per cubic millimeter and the leukocyte count 28,100 with 85 per cent polymorphonuclears and 15 per cent small lymphocytes. Wassermann and Kahn tests of the blood gave reactions of 2 plus. Urinalysis revealed no abnormalities except for occasional hyaline casts. The Wassermann reaction of the spinal fluid was 4 plus. Three blood cultures yielded no organisms.

Course.—Petechiae appeared in the conjunctivas. Fever (99 to 102 F.) continued. On March 28 left hemiplegia developed suddenly (embolism). Coma ensued, terminating in death the following day. The diagnosis was: syphilitic aortic insufficiency, bacterial endocarditis, syphilitic aortitis and neurosyphilis.

Autopsy (performed by Dr. P. Melnick).—The heart weighed 465 Gm. The aortic leaflets were shrunken and thickened and presented numerous gray-red, granular vegetations. Similar vegetations were observed on the anterior wall of the left ventricle. The commissures separating the aortic leaflets were widened. The aorta showed marked wrinkling and puckering of the intima. Culture of the spleen yielded Str. viridans.

The pathologic diagnosis was: malignant vegetative endocarditis of the aortic valve and mural endocarditis of the adjacent endocardium, syphilitic aortitis and syphilitic aortic insufficiency.

CASE 7.—J. O., a white man, aged 54, was admitted to the Cook County Hospital on March 30, 1931. Eleven days before entrance he had a chill followed by fever, pain in the right side of the chest, shortness of breath and cough with expectoration of a thick, tenacious bloody sputum. The pain in the chest was intensified by deep inspiration and by coughing.

Past History.—The patient had gonorrhea at 24 years of age but said he had not had syphilis. The rest of the history was irrelevant.

Physical Examination.—The man was well developed and well nourished, slightly dyspneic, cyanotic and acutely ill. The temperature was 102 F. (rectal); the pulse rate was 108, and the respiratory rate 28, per minute. The pupils were unequal and slightly irregular, but reacted to light and in accommodation. The pharynx was hyperemic. Examination of the lungs revealed dulness, increased tactile fremitus, bronchial breathing, whispered pectoriloquy, and subcrepitant rales over the upper lobe of the right lung. The heart was normal. The liver was palpated 2 cm. below the costal margin on inspiration. The patellar reflexes were sluggish, and the achilles tendon reflexes absent. The rest of the examination gave negative results.

Laboratory Examination.—Urinalysis revealed no abnormalities. The Kahn reaction of the blood was 1 plus. The leukocytes numbered 10,600 per cubic millimeter.

Course.—The temperature dropped to normal on April 6 but rose again on the following day. The pulse and respiration became accelerated, and gross hematuria appeared. Urinalysis showed the urine to be acid and to have a specific gravity of 1.012. There was a 2 plus reaction for albumin, and no sugar was present. Myriads of erythrocytes and occasional leukocytes were observed microscopically. On April 19 a to and fro murmur was audible at the apex and the base. The findings with reference to the lungs were unchanged. The temperature ranged from 98 to 103.6 F. (rectal); the respirations were 24 to 28 per minute. Death occurred on April 20. The diagnosis was: unresolved pneumonia, bacterial endocarditis and neurosyphilis (?).

Autopsy (performed by Dr. S. Rosenthal).—Gross Examination: The heart weighed 415 Gm. The right aortic cusp was perforated by a polypoid, yellow-gray soft mass 1.5 by 0.2 cm. The first portion of the aorta presented numerous elevated, firm, grayish plaques showing wrinkling and puckering, especially in the commissures.

Microscopic Examination: The aorta showed subendothelial intimal thickening with round cell infiltration. There were numerous perivascular and focal round cell infiltrations in the adventitia and the media as well as scarring and rupture of the elastic lamina.

The pathologic diagnosis was: postpneumonic thromboulcerative endocarditis of the aortic valve, syphilitic aortitis, syphilitic aortic insufficiency and lobar pneumonia of the upper lobe of the right lung, complicated by carnification and abscess.

Other Cases.—In 3 other instances of this series, bacterial endocarditis had developed on previously damaged aortic valves and was associated with syphilitic aortitis, but in the absence of a positive statement regarding the condition of the commissures they could not be accepted as proved instances of syphilitic aortic insufficiency. Similarly, I have not included in the reports the instance of subacute bacterial endocarditis engrafted on a congenital bicuspid aortic valve showing also the typical signs of syphilitic valvular involvement and associated with syphilitic aortitis, since bicuspid aortic valves are more often complicated by endocarditis than are syphilitic valves.

COMMENT

Incidence.—While the literature is replete with comments relative to the rarity with which bacterial endocarditis develops on syphilitic aortic valves, with few exceptions, little indication of the approximate incidence may be gleaned from the reports available at present. Thus, in a series of 198 cases of bacterial endocarditis, Thayer [13] noted only 1 instance of acute endocarditis superimposed on syphilitic valves. Smith [24] observed a single instance (acute) in a series of 193 cases (acute and subacute), and recently Martin and Adams [26] reported 2 instances among 157 cases of subacute bacterial endocarditis collected from a total of 17,000 cases in which necropsy was performed. A further attempt to answer this question was made in the present study.

Of a total of 241 proved cases of subacute bacterial endocarditis collected from the records of the Cook County and the Michael Reese Hospital, in 5 the disease was observed to be engrafted on a preexisting uncomplicated syphilitic valvular deformity (2.1 per cent). These cases were selected from a series of 14,809 cases in which necropsy was done, the incidence being, therefore, 0.03 per cent. Although but few contributors to the literature have designated the number of cases of bacterial endocarditis observed at necropsy from which their studies were drawn, the available data (table 4) indicate that these combined lesions occurred in 7 of 590 instances of subacute bacterial endocarditis. Addition of the total necropsy figures of Martin and Adams [26] to those of the present report shows only 7 such instances among 31,809 cases in which autopsy was performed (0.02 per cent) (table 4).

A complete study of the cases of acute bacterial endocarditis observed at the Michael Reese Hospital could not be made, but a review of the necropsy records of syphilitic aortitis revealed only 1 instance

of unquestionable syphilitic aortic insufficiency complicated by acute bacterial endocarditis. Another case was found in the records of the Cook County Hospital among 31 instances of acute bacterial endocarditis. While this form of endocarditis is much less common than the subacute type, the limited material available indicates that it involves syphilitic valves with the same frequency as does the subacute variety (table 4).

The explanation of the infrequent involvement of syphilitic valves by bacterial endocarditis has evoked much thought and speculation. Briggs [10] expressed the opinion that age incidence plays a significant role, since both rheumatic heart disease and bacterial endocarditis are more common among persons under the age of 35 years, whereas

TABLE 4.—*Incidence of Bacterial Endocarditis and Syphilis of the Aortic Valve*

		Acute Bacterial Endocarditis			Subacute Bacterial Endocarditis			
			Cases Engrafted on Syphilitic Valves			Cases Engrafted on Syphilitic Valves		
Author	Total Number of Necropsies	Total Number of Cases	No.	%	Total Number of Cases	No.	%	% of Total Number of Necropsies
Thayer	.....	177	1	...	21	0	...	....
Smith	.....	22	1	...	171	0	...	....
Martin and Adams	17,000	..	..	...	157	2	...	....
Rosenberg	14,809	32	2	...	241	5	...	....
	31,809	231	4	1.7	590	7	1.3	0.02

syphilitic cardiovascular disease usually becomes manifest in older persons. Attractive as this idea may appear, the interpretation seems to be more subtle.

Perry [28] suggested that the comparative rarity of syphilitic heart disease, as observed in the principal teaching hospitals in Great Britain, might in itself be explanatory. But this view seems inadequate, for in the United States, among persons over 40 years of age syphilis is a common cause of aortic insufficiency. Perry postulated further that perhaps the shorter duration of life of patients with syphilitic heart disease, as compared with that of patients with rheumatic heart disease, presents fewer opportunities for the development of bacterial endocarditis. While this may be a factor, one must be reminded that even though the life expectancy is short once the symptoms of cardiovascular syphilis appear, the development of this advanced stage is long and insidious.

Another point of view has evolved from the belief, held by some investigators, that rheumatic fever and subacute bacterial endocarditis are but manifestations of the same infection and that this accounts for

their frequent association. Von Glahn and Pappenheimer [38] reviewed the literature pertaining to this aspect of the subject and from their studies concluded that subacute bacterial endocarditis arises as a secondary bacterial infection implanted on unhealed rheumatic verrucae. Other investigators are in accord with the belief that these two diseases are of different origins. Indeed, the very occurrence of subacute bacterial endocarditis on syphilitic valves, even though rare, is another point in favor of the latter view; yet, on the other hand, it may bespeak the factor of coincidence.

Basing his conclusion on Koester's [39] view that infections of the valves of the heart arise from bacterial emboli lodging in the coronary capillaries, Briggs [10] stated that the greater vascularization of rheumatic valves offered a cogent explanation for the higher incidence of subacute bacterial endocarditis in rheumatic hearts. In support of Koester's belief, Bayne-Jones [40] observed an increased vascularity in the valves damaged by the rheumatic virus. In his injection experiments, however, he noted that the increased network of capillaries reached the edges of the auriculoventricular valves, but ended along the basal part of the semilunar valves. These studies afford a feasible explanation for the susceptibility of rheumatic mitral valves to bacterial endocarditis but not for that of rheumatic aortic valves. The fact that one can also demonstrate an increased vascularity in syphilitic aortic valves detracts further from Briggs's hypothesis. Moreover, one cannot reconcile this view with the observation that bicuspid aortic valves, more often affected by subacute bacterial endocarditis than are syphilitic valves, show no increased vascularization (Perry [23]) nor with Keefer's [32] failure to demonstrate blood vessels in the valves of the heart of all subjects.

Saphir and Wile [41] offered the explanation that the deformity of the aortic valves produced by syphilis results in decreased excursions of the cusps, thereby providing smaller areas for the settling of bacteria. In contrast, they stated that in cases of rheumatic and congenital diseases the aortic valves present larger areas than normal for bacterial implantation. This interesting observation has heretofore received

38. Von Glahn, W. C., and Pappenheimer, A. M.: Relationship Between Rheumatic and Subacute Bacterial Endocarditis, Arch. Int. Med. **55**:173 (Feb.) 1935.

39. Koester, K.: Die embolische Endocarditis, Virchows Arch. f. path. Anat. **72**:257, 1878.

40. Bayne-Jones, S.: The Blood Vessels of the Heart Valve, Am. J. Anat. **21**:449 (May) 1917.

41. Saphir, O., and Wile, S. A.: Rheumatic Manifestations in Subacute Bacterial Endocarditis in Children, Am. Heart J. **9**:29 (Oct.) 1933.

no consideration. Nevertheless, it would seem to be a contributory factor.

A review of the present state of knowledge indicates that bacterial endocarditis arises usually as a surface infection, invading the valves from without. Leary [42] and Mallory and Keefer [43] were able to demonstrate this experimentally. Further, Grant, Wood and Jones [44] often observed platelet thrombi adherent to damaged heart valves and expressed the opinion that such thrombi, relatively free from leukocytes, form an ideal nidus for the localization and growth of bacteria. The importance of leukocytes as an effective and rapid bactericidal agent has recently been clearly demonstrated by Friedman, Katz and Howell [45] in their experimental study of endocarditis due to Str. viridans. It is of special interest then, that Grant, Wood and Jones [44] observed platelet thrombi more commonly in rheumatic valvular disease and on congenitally diseased bicuspid aortic valves and only infrequently in syphilitic valvular disease. They attributed this difference in part to the degenerative changes so often occurring in their cases in which there were rheumatic and congenitally defective bicuspid valves and not to thickening of the valves alone, for the latter likewise occurs in syphilitic valves.

Keefer [32] pointed out that in the development of bacterial endocarditis four factors are important, namely: (1) a previously damaged valve, (2) platelet thrombi on the valves, (3) transient bacteremia and (4) antibacterial antibodies, the presence of which favors localization of bacteria. While the problem is obviously a complex one, it would seem that further immunologic study might aid in the interpretation of the low incidence of syphilitic valvular disease complicated by bacterial endocarditis. Once bacteria become entangled in platelet thrombi, the immunologic factor appears to assume secondary importance.

Bacterial Endocarditis and Syphilitic Aortitis per Se.—In recent years much confusion has arisen in the literature concerning the development of bacterial endocarditis in patients with syphilitic aortitis without syphilitic involvement of the aortic cusps and commissures. Most authors have inferentially regarded this combination as rare. In a large measure, this deduction has resulted from the failure to distinguish this combination from that of bacterial endocarditis engrafted on

42. Leary, T.: Early Lesions of Rheumatic Endocarditis, Arch. Path. **13**:1 (Jan.) 1932.

43. Mallory and Keefer, cited by Keefer.[32]

44. Grant, R. T.; Wood, J. E., and Jones, T. D.: Heart Valve Irregularities in Relation to Subacute Bacterial Endocarditis, Heart **14**:247 (Aug.) 1928.

45. Friedman, M.; Katz, L. N., and Howell, K.: Experimental Endocarditis Due to Streptococcus Viridans: Biologic Factors in Its Development, Arch. Int. Med. **61**:95 (Jan.) 1938.

syphilitic deformities of the aortic leaflets. Moreover, the erroneous impression conveyed by earlier writers has often been merely recapitulated but not subjected to critical inquiry. Thayer [13] observed 2 instances of syphilitic aortitis in his series of cases of bacterial endocarditis of the aortic valve but justly disregarded the aortitis as a predisposing factor, for in the one instance, evidence of antecedent valvular disease was lacking, and in the other, the valvular defect was "in all probability" rheumatic in origin.

Skursky,[17] François and Jouve,[30] Raybaud, Jouve and Farnarier [28] and Gallavardin and Gravier [27] stressed the rare occurrence of subacute bacterial endocarditis in patients with syphilitic aortitis per se but presented no statistical data. They recorded isolated instances to emphasize their contention. Raybaud and Jouve [46] reviewed the literature dealing with subacute bacterial endocarditis and syphilis and arrived at the same conclusion. However, they too failed to differentiate the instances of bacterial endocarditis complicating syphilitic valvular disease from those of bacterial endocarditis associated with syphilitic aortitis alone. Latterly, Smith,[24] in his review, reiterated the earlier opinions, stating that the "combination" of syphilitic aortitis and bacterial endocarditis is "decidedly rare," and reported 2 such cases. In the one, syphilitic aortitis was associated with acute endocarditis of the aortic valve due to Staph. aureus, the aortic cusps being otherwise normal; in the other, it was associated with rheumatic aortic stenosis complicated by endocarditis of the aortic valve due to Str. viridans. It is at once apparent that these cases differ materially from those constituting the subject of this paper and that a distinction must always be made.

From the present study it is evident that the concomitance of syphilitic aortitis and bacterial endocarditis is in reality not rare, since it was found in 19 instances in this series of 273 cases of bacterial (acute and subacute) endocarditis in which necropsy was done, an incidence of 7 per cent. In 7 of these 19 there was syphilitic valvular disease, and these 7 cases form the basis of this report. Of the remaining 12, in 4 the antecedent aortic valvular deformity was rheumatic in origin; in 4 the recent endocarditis did not develop on the aortic valves (3 on rheumatic mitral defects, 1 on a normal pulmonic valve); in 3 the nature of the earlier deformity of the aortic valves was not clear from the descriptions in the protocols, and in 1 the endocarditis had developed on coexisting congenital and syphilitic defects of the aortic cusps. Thus, in many instances, syphilitic aortitis may be but an incidental observa-

46. Raybaud, A., and Jouve, A.: De la coexistence au niveau de la région sigmoïdienne aortique de lésions syphilitiques anciennes et d'une endocardite maligne à évolution lente ou subaiguë, Ann. de méd. **39**:211 (Feb.) 1936.

tion in the course of bacterial endocarditis, bearing no relationship to its development. Singularly illustrative of this, is an instance (case 741; 1934) in which the syphilitic changes in the aorta extended to the commissures, yet the lesions of subacute bacterial endocarditis had developed on a preexisting rheumatic aortic stenosis. As a corollary to this, it becomes clear that diagnosis on the basis of necropsy evidence alone should be regarded as conclusive and that syphilitic aortitis assumes importance as a possible predisposing factor to bacterial endocarditis only when the syphilitic process has extended to produce a deformity of the aortic valve.

Diagnosis.—The clinical recognition of syphilitic aortic valvular disease, when complicated by bacterial endocarditis, may be fraught with much difficulty, especially if the initial examination is performed after the endocarditis has become manifest. Of paramount importance is an appreciation of the vulnerability of syphilitic valves to subsequent bacterial endocarditis, however rarely this combination may be encountered. Accordingly, a conscious effort must be made to exclude syphilitic valvular disease in all patients exhibiting bacterial endocarditis with aortic insufficiency. Although age, per se, does not preclude syphilitic valvular disease, even in patients in the third decade of life, nevertheless, in persons under 35 years of age, the underlying disease is more likely to be rheumatic. A careful anamnesis with special reference to syphilis as well as to the most common predecessor of bacterial endocarditis, namely, rheumatism in its various forms, in conjunction with a comprehensive physical examination, is most essential. Signs of organic mitral stenosis, while at times indistinguishable from a Flint murmur, suggest the rheumatic type of aortic insufficiency, whereas an accentuated, ringing second aortic sound points to syphilis as a cause. As cardiovascular syphilis is frequently accompanied by involvement of the central nervous system (an incidence as high as 54 per cent in the Mayo Clinic series, according to Stokes [37]), the value of a carefully conducted neurologic study cannot be overemphasized. Pupillary and reflex changes, in particular, may direct attention to the possibility of underlying syphilis, and tests of the spinal fluid may provide confirmatory evidence. Indeed, in case 1 of the present series the diagnosis of syphilitic aortic insufficiency was first suspected from the absence of the achilles tendon reflexes coupled with the irregularity of the pupillary reflexes. But even in the presence of syphilis, aortic regurgitation may be due to simple dilatation of the aortic ring secondary to syphilitic aortitis rather than to valvular deformity or to an antecedent rheumatic or congenital disease (as already mentioned), and in such instances a correct clinical diagnosis along rational lines may not be possible.

The diagnostic significance of a positive Wassermann reaction in cases of subacute bacterial endocarditis merits more than passing comment. Landau and Held [47] reported positive reactions in 10 of 30 cases of endocarditis lenta. Of these 10 cases, 6 presented neither clinical evidence, nor a history, of syphilis, and in 4 of the 6 cases, no anatomic signs of syphilis were observed at necropsy. The positive reactions in these 6 cases were interpreted as incidental and secondary to a "disturbed colloid or lipoid balance in the serum." Fulton and Levine [20] reviewed 111 clinical cases of subacute bacterial endocarditis, and, although in 9 there were positive Wassermann reactions, only 1 could be regarded as a case of syphilitic aortic insufficiency. Stokes [37] said that he had encountered at least 8 cases of strongly positive Wassermann reactions of the blood "with endocarditis manifestations, obviously of a septicemic or subacute bacterial type," and remarked that the occurrence of false positive serologic reactions in instances of subacute bacterial endocarditis may be accepted as established. He also alluded to the findings of E. Meyer,[48] who observed at the Goettingen Clinic 7 of 20 cases in which there were positive reactions. Wydrin [49] said that he concurred with this opinion but that he observed that of 50 cases of subacute bacterial endocarditis, in 4 there were positive reactions, and in only 1 of these were anatomic signs of syphilis lacking. Heilig [50] obtained positive reactions in 8 of 213 clinical cases of subacute bacterial endocarditis, and in none was there a history of syphilis. Grossman [51] noted similar reactions in 4 of 21 cases, but no details were reported. These observations indicate that in the absence of syphilis a positive Wassermann reaction may occur occasionally in cases of this disease. Hence, should the patient state that he has never had syphilis and should a meticulous search reveal no signs of syphilis, the connotation of consistently positive reactions must be held in doubt. Perhaps other serologic tests, such as the Kahn and the Hinton test, together with the Wassermann test of the spinal fluid and the colloidal gold chloride test, may prove helpful.

As bacterial endocarditis more commonly attacks the rheumatic heart, it is necessary at necropsy to differentiate rheumatic from syphilitic aortitis, for the two may be confounded anatomically. From their

47. Landau, A., and Held, J.: Sur la réaction dê Bordet-Wassermann positive au cours de l'endocardite lente, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1322 (Oct. 9) 1925.

48. Meyer, E., cited by Stokes.[37]

49. Wydrin, A: Bakteriämie, Wassermann-Reaktion und morphologisches Blutbild bei Endocarditis lenta, Wien. Arch. f. inn. Med. **25**:231, 1934.

50. Heilig, F., cited by Wydrin.[49]

51. Grossman, S., cited by Wydrin.[49]

studies on the histologic changes in rheumatic aortitis, Klotz [52] and Pappenheimer and Von Glahn [53] concluded that in syphilis the following conditions exist: The perivascular cellular infiltrations are greater, the scars are more extensive, many new capillaries are seen in the affected areas, and the intimal lesions are more frequent and more marked than in rheumatism. Further, in some cases of rheumatic aortitis, cellular infiltrations typical of, or resembling, Aschoff cells, may be seen (Pappenheimer and Von Glahn [53]) and, if present, may be regarded as of diagnostic value.

Finally, it is probable that with greater attention devoted to the condition of the aortic commissures one may find syphilis of the aortic valve and bacterial endocarditis coexistent more frequently than has hitherto been appreciated.

SUMMARY

The literature dealing with bacterial endocarditis and syphilitic valvular disease is critically reviewed, and the reported cases are grouped categorically as proved, doubtful and unproved.

Since Libman first directed attention to the infrequent concurrence of these diseases, only 10 proved cases have been reported. To these, the records of 7 more instances are added, making a total of 17 proved cases. Of the remaining cases in the literature, 4 are regarded as doubtful, and in 29 the existence of syphilitic aortic valvular disease remains unproved.

Based on the available data, a study of the incidence is made, and the suggestions offered for the interpretation of the rarity of this combination are discussed. Attention is drawn to the diagnostic difficulties and to the limitations of a positive Wassermann reaction.

Contrary to the opinions expressed in current literature, it is apparent from this study that bacterial endocarditis associated with syphilitic aortitis per se (without involvement of the aortic cusps or commissures) is not of rare occurrence.

With greater interest directed to the clinical and anatomic recognition of bacterial endocarditis superimposed on syphilitic valvular deformities, it is likely that their coexistence may be observed more frequently than heretofore.

The cooperation of Dr. Otto Saphir was of valuable assistance in this study. Dr. Walter Schiller gave permission for the study of the necropsy material at the Cook County Hospital.

52. Klotz, O.: Rheumatic Fever and the Arteries, Tr. A. Am. Physicians **27**:181, 1912.

53. Pappenheimer, A. M., and Von Glahn, W. C.: Lesions of the Aorta Associated with Acute Rheumatic Fever and with Chronic Cardiac Disease of Rheumatic Origin, J. M. Research **44**:489 (Sept.) 1924.

SURVEY OF DIABETES

STATISTICAL DATA AND CONTROL COMPARISONS WITH VARIOUS INSULINS

BERTNARD SMITH, M.D.
AND
WILLIAM H. GRISHAW, M.D.
LOS ANGELES

The data presented in this report are from the records of 800 diabetic patients who have been under our observation for one or more years. Laboratory analyses were performed at such intervals as would furnish reliable opinions regarding diabetic control. All of these patients are ambulatory. The series includes patients in our diabetic clinics for both adults and children, as well as private patients.[1]

For convenience in arranging the mass of data from this number of records the patients have been divided into two groups, according to the nature of the onset of diabetes. Those who experienced the sudden onset of excessive thirst, polyuria and rapid loss of weight and strength before the diagnosis of diabetes was made are classed as having diabetes of acute onset. Patients who have had none of these symptoms in acute form at onset are classed as having diabetes of gradual onset. In the group with diabetes of gradual onset, the disease was discovered in routine insurance or health examinations or in a physical examination for some suspected disease other than diabetes. In both groups the patients are listed as juvenile when the onset of diabetes occurred while the patient was under 16 years of age.

The terms in all tables are defined as follows:

Severe diabetes.....Diabetes requiring 40 units of insulin or more

Moderately severe diabetes..Diabetes requiring 20 to 40 units of insulin

Mild diabetes.....Diabetes requiring 20 units of insulin or less

Based on diets containing 150 Gm. of carbohydrate

Good control.....20 Gm. or less of sugar in urine in twenty-four hours

1. Clinic patients have been selected from the outpatient diabetic clinics of the Cedars of Lebanon Hospital and the Children's Hospital.

Fair control.....20 to 40 Gm. of sugar in urine in twenty-four hours

Poor control.....40 Gm. or more of sugar in urine in twenty-four hours

R-I .....Regular amorphous insulin

ZP-I .....Protamine zinc insulin

CZ-I .....Crystalline zine insulin

TABLE 1.—*Classification of Patients with Diabetes of Gradual Onset*

Diabetes	Adult		Juvenile		Totals
	Gentiles	Jews	Gentiles	Jews	
Severe	12	1	4	0	17
Moderately severe	58	46	12	0	116
Mild	108	164	0	0	272
					405

TABLE 2.—*Data on Patients with Diabetes of Gradual Onset*

Years Observed		Age at Onset	
1 to 2	43	0- 9	6
2 to 3	65	10-19	10
3 to 4	56	20-29	16
4 to 5	55	30-39	56
5 to 10	146	40-49	134
10 to 15	28	50-59	112
15 to 20	9	60-69	62
20 to 25	3	70-79	9
	405		405

DIABETES OF GRADUAL ONSET

Of the total of 800 patients, 405 were found to belong in the group with diabetes of gradual onset. Of this number, only 16 were of juvenile age at onset. In table 1 it is shown that 67 per cent of the 405 patients with diabetes of gradual onset have a mild form of diabetes, and of these 60 per cent are Jewish. In table 2, with patients grouped as to age at onset, it is seen that in 60 per cent of the group with diabetes of gradual onset, diabetes was discovered between the ages of 40 and 60 years.

In 60 patients of the group with diabetes of gradual onset no organic disease was found in the routine examination that revealed glycosuria for the first time. All of these 60 patients have continued to show a mild

degree of diabetes. In 98 patients the following conditions were present when diabetes was first found:

	No of Patients
Organic cardiovascular disease	76
Carcinoma	3
Pyelitis, acute	5
Hypertrophy of prostate, benign	9
Hyperthyroidism	5
Hypothyroidism	4
Gallstones	7
Bronchial asthma	5
Pulmonary tuberculosis	5
Appendicitis, acute	7
Infection of upper respiratory tract, acute	13
Menopause	7
Pregnancy	5
Retinal arteriosclerosis, advanced	19
Furunculosis	6
Renal stone	1
Accident, with fracture	3
Syphilis	2
Spastic colitis	4
Mammary tumor, benign	3
Mastoiditis, acute	3
Tonsillitis, acute	3
Otitis media	2
Enteritis, acute	3
Bronchopneumonia	1
Measles	1
Mumps	1

In these 98 patients the severity of the diabetes is in direct proportion to the continued severity of the complication found at onset. The 19 patients who had advanced retinal arteriosclerosis at onset have shown a gradual increase in the severity of their diabetes during several years of observation, but insulin therapy has been prescribed in moderation. These patients are of advanced age, with general arteriosclerosis, and require protective therapy.

OBESITY

Of the 405 patients with diabetes of gradual onset 247 were obese when glycosuria was first noted. Private patients (133) averaged 37.9 pounds (17 Kg.) above the normal weight, and clinic patients (114) averaged 53.3 pounds (24 Kg.) above normal. Of this group of 247 obese patients, 140 were Jewish and 107 gentiles. Males numbered 83 and females 164. Eight patients were 100 pounds (45.4 Kg.) or more above their normal weight; of these, 2 were males and 6 females. In none of these cases of obesity was there found any cause of excess weight other than overeating. Body weights recorded in January 1939 show an average loss of weight since onset of diabetes of 36.3 pounds (16 Kg.) for 133 private patients and of 47.2 pounds (21 Kg.) for 114 clinic patients. In table 3 we present a comparison of the severity of diabetes in these obese patients at onset and at the time of writing. The improvement shown in this table is proportionate to the loss of weight. Of the 247 obese patients, 136 have required insulin. Of this number, only 30 have stopped taking insulin and maintained full diabetic control on diet alone. However, there are 52 patients who continue to take

insulin once daily in doses of 4 to 8 units, and this has been continued only as an aid to better cooperation for further loss of weight.

Of the 405 patients with diabetes of gradual onset, 225 have required insulin. Of this number, 76 have been able to stop using insulin and have maintained good diabetic control on diet alone. Table 4 is a comparative study of control with the various forms of insulin. Of 225 patients treated with insulin, 158 began with the regular amorphous insulin; 55 began with protamine zinc insulin alone, 5 patients taking two injections daily; 2 patients began with a combination of regular and protamine zinc insulin, both taken each morning, and 10 patients began with crystalline zinc insulin, taking two injections daily. Patients

TABLE 3.—*Effect of Loss of Weight on Two Hundred and Forty-Seven Obese Diabetic Patients*

Diabetes at Onset		Diabetes at Present	
Severe	0	Severe	0
Moderately severe	79	Moderately severe	32
Mild	168	Mild	215

TABLE 4.—*Comparative Control with Various Insulins (Two Hundred and Twenty-Five Patients with Diabetes of Gradual Onset)*

Diabetes	R-I Control	ZP-I Alone	R-I and ZP-I	CZ-I Alone	CZ-I and ZP-I
Severe	Good 11	Good 0	Good 6	Good 5	Good 4
	Fair 3	Fair 4	Fair 6	Fair 1	Fair 2
	Poor 8	Poor 1	Poor 5	Poor 0	Poor 0
Moderately severe	Good 44	Good 17	Good 12	Good 14	Good 7
	Fair 18	Fair 19	Fair 5	Fair 2	Fair 0
	Poor 14	Poor 22	Poor 5	Poor 0	Poor 0
Mild	Good 42	Good 68	Good 2	Good 34	Good 0
	Fair 12	Fair 32	Fair 1	Fair 0	Fair 0
	Poor 6	Poor 3	Poor 0	Poor 0	Poor 0

maintaining good diabetic control with any insulin were not changed to another insulin unless there was need for fewer injections or a change was requested for purposes of insulin study. At present 96 patients using protamine zinc insulin alone and 28 of the 34 mildly diabetic patients using crystalline zinc insulin alone are able to maintain full diabetic control with one daily injection. The 13 patients (table 4) receiving both crystalline and protamine zinc insulin have been most difficult to hold in moderate control with regular insulin and with regular insulin and protamine zinc insulin combined. At present these patients are taking both insulins in morning injections.

DIABETES OF ACUTE ONSET

Of the 800 patients, 395 had an acute onset of excess thirst, polyuria and rapid loss of weight and strength before the diagnosis of diabetes was made. These symptoms were severe in all of the 395 patients and

were given as the reason for the requested examinations in which diabetes was discovered. The interval between the onset of symptoms and the diagnosis of diabetes ranged from a few hours to several months. Longer delays in diagnosis caused many of the patients of this group to be first examined when in extreme ketosis and coma. However, the experience of the last few years indicates that an earlier diagnosis of diabetes is being made, with a marked decrease in the number of new patients who are first seen in coma.

Of the 395 patients with diabetes of acute onset, only 2 were overweight at onset. Twenty patients of this group have never required insulin, and 1 of these was of juvenile age at the time of onset. Only

TABLE 5.—*Classification of Patients with Diabetes of Acute Onset*

Diabetes	Adult		Juvenile		Totals
	Gentiles	Jews	Gentiles	Jews	
Severe	33	21	62	17	133
Moderately severe	73	38	78	5	194
Mild	31	28	8	1	68
					395

TABLE 6.—*Data on Patients with Diabetes of Acute Onset*

Years Observed	Adult	Juvenile	Age at Onset	
1 to 2	16	19	0- 9	96
2 to 3	22	21	10-19	88
3 to 4	26	23	20-29	61
4 to 5	36	32	30-39	54
5 to 10	58	46	40-49	57
10 to 15	44	21	50-59	33
15 to 20	21	9	60-69	6
20 to 25	1	..		395
	224	171		

17 per cent of our 395 patients in the group with diabetes of acute onset had a mild degree of diabetes, and of the 224 patients who were of adult age at the time of onset 61 per cent were gentiles. Since the adult clinic is in the outpatient department of a Jewish hospital, this is of interest. Of the patients with diabetes of acute onset, 46.5 per cent were within the first two decades of life at the time of onset. The great majority of this group have diabetes which is severe or is in the more severe range of moderately severe.

Patients of the group with diabetes of acute onset who were of adult age at the time of onset have continued to manifest an acute clinical picture through years of close observation. Marked change in the control may follow very slight changes in diet or in the use of insulin, mild acute infections, nervous and emotional disturbances or changes in physical activity. As would be expected, the great majority of the

diabetic patients who have presented difficult problems in satisfactory and even control belong to the group with diabetes of acute onset.

In the adult group represented in table 7, 174 patients began with the regular amorphous form of insulin; 17 began with protamine zinc insulin alone; 6 began with combined regular and protamine zinc insulins; 7 began with crystalline zinc insulin alone, and 1 began with combined crystalline zinc and protamine zinc insulins.

In the juvenile group represented in table 8, 139 patients began with insulin of the amorphous form; 17 began with protamine zinc insulin

TABLE 7.—*Comparative Control with Various Insulins (Two Hundred and Five Adult Patients with Diabetes of Acute Onset)*

Diabetes	R-I Control	ZP-I Alone	R-I and ZP-I	CZ-I Alone	CZ-I and ZP-I
Severe	Good....12	Good.... 2	Good....14	Good....14	Good....26
	Fair....18	Fair.... 7	Fair....17	Fair.... 8	Fair....18
	Poor....10	Poor....12	Poor.... 9	Poor.... 0	Poor.... 1
Moderately severe	Good....27	Good....12	Good....24	Good....11	Good....21
	Fair....48	Fair....10	Fair....22	Fair.... 2	Fair.... 4
	Poor....26	Poor....15	Poor....15	Poor.... 0	Poor.... 0
Mild	Good....18	Good....14	Good....21	Good....18	Good.... 6
	Fair....10	Fair.... 1	Fair.... 1	Fair.... 0	Fair.... 0
	Poor.... 5	Poor.... 1	Poor.... 0	Poor.... 0	Poor.... 0

TABLE 8.—*Comparative Control with Various Insulins (One Hundred and Seventy Juvenile Patients with Diabetes of Acute Onset)*

Diabetes	R-I Control	ZP-I Alone	R-I and ZP-I	CZ-I Alone	CZ-I and ZP-I
Severe	Good....15	Good.... 3	Good....21	Good.... 5	Good....24
	Fair....22	Fair.... 7	Fair....23	Fair.... 0	Fair....18
	Poor....35	Poor.... 8	Poor....23	Poor.... 0	Poor.... 2
Moderately severe	Good....23	Good.... 6	Good....16	Good.... 4	Good....28
	Fair....27	Fair.... 4	Fair....11	Fair.... 0	Fair.... 0
	Poor....12	Poor....13	Poor.... 6	Poor.... 0	Poor.... 0
Mild	Good.... 5	Good.... 2	Good.... 0	Good.... 0	Good.... 0
	Fair.... 0	Fair.... 2	Fair.... 0	Fair.... 0	Fair.... 0
	Poor.... 0	Poor.... 0	Poor.... 0	Poor.... 0	Poor.... 0

alone; 6 began with combined regular and protamine zinc insulins; 7 began with crystalline zinc insulin alone, and 1 began with combined crystalline zinc and protamine zinc insulins. As with the patients of the group with diabetes of gradual onset who are taking insulin, none of the patients in the group with diabetes of acute onset were changed from any form of insulin that gave good control unless the convenience of fewer injections was of importance or insulin studies were requested. Only a few of the juvenile group with diabetes of acute onset have been observed while taking crystalline zinc insulin alone for sufficient time to be included in this report.

The records of 50 adult and 50 juvenile patients have been selected for comparison. These are among the more severely diabetic patients

of the group with diabetes of acute onset. Control comparisons were made with regular insulin, regular and protamine zinc insulins combined and crystalline zinc and protamine zinc insulins combined. The combined insulins were given in the morning only, but by separate injections. In table 9 are shown the degree of control with the various changes and the change in the unit dose of insulin required. The change in the unit dose of regular insulin and protamine zinc insulin combined is compared with that required with regular insulin alone. The daily unit dose of combined crystalline zinc and protamine zinc insulins is compared with that required with combined regular and protamine zinc insulins.

In tables 7 and 8 one sees a definite change in control toward good and fair degrees with combined regular and protamine zinc insulins.

TABLE 9.—*Effect of Changes in the Type of Insulin Used (Fifty Adult and Fifty Juvenile Patients)*

Diabetes	R-I	R-I and ZP-I		CZ-I and ZP-I	
	Control	Control	Dose	Control	Dose
Adults					
Severe.....	Good... 0 Fair....14 Poor...10	Good...11 Fair.... 8 Poor... 5	Decreased.. 5 Same..... 9 Increased..10	Good.....14 Fair..... 9 Poor..... 1	Decreased..16 Same..... 8 Increased.. 0
Moderately severe	Good... 0 Fair.... 0 Poor...26	Good... 8 Fair....12 Poor... 6	Decreased.. 5 Same..... 5 Increased..16	Good.....25 Fair..... 1 Poor..... 0	Decreased..22 Same..... 4 Increased.. 0
Children					
Severe.....	Good... 0 Fair.... 8 Poor...24	Good... 5 Fair....16 Poor...11	Decreased.. 1 Same..... 7 Increased..24	Good.....20 Fair.....11 Poor..... 1	Decreased..23 Same ..... 6 Increased.. 3
Moderately severe	Good... 0 Fair.... 8 Poor...10	Good... 1 Fair....10 Poor... 7	Decreased.. 2 Same..... 5 Increased..11	Good.....11 Fair..... 6 Poor..... 1	Decreased.. 8 Same..... 4 Increased.. 6

This becomes more satisfactory after a change to the crystalline form, either alone in two daily doses or in combination with protamine zinc insulin, with both insulins taken in the morning. Protamine zinc insulin used alone, in either one or two injections daily, has not been satisfactory in our experience except with mild diabetes or the milder range of moderately severe diabetes. The improved control secured with the change to crystalline zinc insulin or to combined crystalline zinc and protamine zinc insulins is even more satisfactory than can be shown by tabulation, since the cases in which the different insulin changes have been carried through have always presented the more difficult problems. An additional point in an estimation of improvement of diabetic control is shown in table 9, under the unit requirement of insulin for each form. In this table the unit dose has been given as the total number of units for the two forms of insulin used. Control with regular insulin alone requires three and often four injections of insulin daily for most of the adult and all of the juvenile patients in the selected group. With a

change to combined regular and protamine zinc insulins there is observed an improved control, with an increase in the number of patients in the "fair" and "good" grades. However, this improvement is seen to have been obtained by an increase in the dose of insulin, in a majority of the cases in the group. Efforts to improve control by giving protamine zinc insulin each morning and regular insulin either in the morning and at noon or in the morning and in the evening have not brought about any satisfactory change.

With crystalline zinc and protamine zinc insulins given each morning there is a definite improvement in control, with an associated decrease in the total unit requirement of insulin. The increases in units of insulin when combined regular and protamine zinc insulins are used are found to be mainly increases in unit dose of the protamine zinc form. Also, decreases in the unit dose of insulin when combined crystalline zinc and protamine zinc insulins are used are largely decreases in the dose of the protamine zinc form. This indicates some fault in the duration of effect of at least one form of insulin when two forms were combined.

Information in regard to the duration of the effect of insulin (regular, crystalline zinc and protamine zinc forms) was desired for clinical application especially to the problems indicated in table 9, in which the increases in unit dose of protamine zinc insulin were entirely out of proportion to those of regular insulin. Studies of the blood sugar were planned to include crystalline zinc insulin, with the same general technic that was followed in studies with precipitated insulins in 1936.[2]

ONSET AND DURATION OF THE EFFECT OF INSULIN AS MEASURED BY THE LEVEL OF BLOOD SUGARS

The composite graph (chart 1) shows the onset and duration of effect measured by the averaged values for blood sugar obtained from the 20 patients studied with three forms of insulin. With the morning dose of the amorphous form of insulin the patient loses the effect soon after noon. Consequently, patients with severe diabetes do not remain under insulin control through the afternoon when such control depends on a morning injection of regular insulin. An effect from the morning

2. Twenty patients with severe diabetes of acute onset were hospitalized for study. No changes were made in the diets except that all patients were given 15 Gm. of carbohydrate as a midnight feeding. Adjustment periods of at least one week were allowed before each test day, and at least moderate diabetic control was secured during this time, usually by the aid of regular insulin. On test days, "micro blood sugars" were obtained before the morning insulin was given, thirty and sixty minutes after breakfast and each hour afterward until an uncontrolled rise in the level of blood sugar indicated loss of the effect of insulin. All insulin on the test days was given thirty minutes before breakfast and in the unit dose estimated as the requirement for each patient from observations made in the adjustment period.

dose of protamine zinc insulin is not obtained until late in the afternoon but continues from the time of onset throughout the night, terminating on the average at 6 a. m., which is nearly twenty-four hours after the insulin was injected. It would seem probable (chart 1) that the use of regular and protamine zinc insulins, both taken in the morning, fails to supply insulin during the afternoon hours. The result of this blank period is an increase of glycosuria and hyperglycemia in the severely diabetic patient. The unit dose of protamine zinc insulin is expected to correct the afternoon disturbance and furnish available insulin for the entire night. This leads to an increase in unit dose of the slowly acting insulin that is much greater than what should be needed for the twelve hours of the night.

The curve in chart 1 shows that a morning dose of crystalline zinc insulin has an effect at onset that is nearly as early as that of amorphous insulin and endures into the late afternoon, terminating on the average at 4 p. m. With our small group of severely diabetic patients crys-

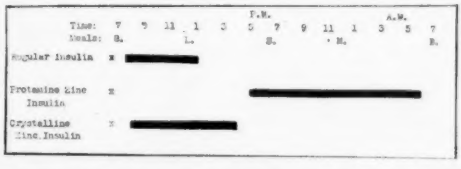

Chart 1.—Onset and duration of the effect of insulin as measured by determination of the level of sugar in the blood. The time of injection of insulin, is represented by *X*; *B* represents breakfast; *L*, luncheon; *S*, supper; *M*, midnight feeding.

talline zinc insulin gives control through the day up to one hour of the time of a beginning supply of insulin from the protamine zinc form. This should enable insulin from the slowly acting form to become available when diabetic control is better maintained, and the excess unit doses of protamine zinc insulin should not be required.

Chart 2 shows curves for the average blood sugar levels in the 20 patients taking regular and crystalline zinc insulins. The evidence of beginning effect of insulin with these two preparations is nearly the same in time, with an average of thirty minutes' delay with the crystalline form. The curve with regular insulin shows a more rapid depression of the level of blood sugar during the second and third hours after breakfast than is obtained with crystalline zinc insulin. The maximum depression of the concentration of blood sugar from the amorphous insulin was observed six and one-half hours after injection of regular

insulin and nine and one-half hours after injection of crystalline zinc insulin. For the small group with severe diabetes crystalline zinc insulin furnished available insulin three hours longer than did regular insulin (for an average of 20 cases). In none of the 20 patients studied was there found any complication that might affect the duration of the effect (during the period of observation in the hospital). The range in termination of insulin control for the crystalline zinc form was found to be from one to four hours longer than for the regular amorphous insulin.

COMMENT

The 800 patients included in this report were found to be equally divided into those with diabetes of acute onset and those with diabetes

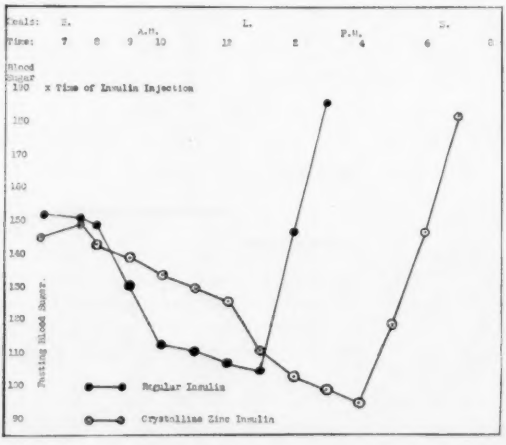

Chart 2.—Blood sugar curves after administration of regular insulin and of crystalline zinc insulin. *B*, breakfast; *L*, luncheon; *S*, supper.

of gradual onset. Many of these patients have been under our observation for several years, and the majority of the juvenile group have been under our care since the onset of their diabetes. No claims are made for the significance of the grouping, but some contrasts between the two groups direct attention to the importance of the nature of the onset in all diabetic history taking. Patients previously reported as giving clinical evidence of sensitiveness to insulin are all included in the group with diabetes of acute onset. Patients of this group, even though the onset occurred at adult age, continue to show an acute response to slight changes in diet or insulin routines. Exaggerated loss of diabetic control

may result from mild complications. For the total of 800 patients, the data on the two groups show the following contrasts:

	Acute Onset (395 Patients)	Gradual Onset (405 Patients)
Number overweight at onset	2	247
Number not requiring insulin	20	180
Mild diabetes	17%	67%
Age of onset by decades	1 and 2, 46.6%	4 and 5, 60.7%
Ketosis	Frequent	Rare
Number juvenile at onset	171	16
Per cent Jewish	27.8%	52%
Clinical course	Always acute	Acute episodes rare

In the tables depicting control it is shown that slowly acting insulin has given good results in those patients who have mild diabetes. The insulin requirement of these patients is moderate, and they usually maintain complete control with one morning injection of protamine zinc insulin. Patients whose condition is in the milder range of moderately severe diabetes were usually unable to maintain good diabetic control on one daily injection of the precipitated insulin. Two daily doses of crystalline zinc insulin gave control that was better maintained than that obtained with two daily injections of the amorphous insulin (when the crystalline zinc form was given at an interval of eleven to twelve hours). With evenly maintained control, improvement is manifested as a lengthening of duration of the effect of insulin, and a number of the patients have become listed as mildly diabetic and maintain full diabetic control on a morning dose of the crystalline zinc form alone.

Selection of an insulin routine for patients with severe acute diabetes often requires a period of strict observation. Recognition of any complicating disease is of great importance. Knowledge of home and business environments must be obtained, and the nervous and emotional stability of each patient must be considered. None of our patients with severe diabetes were able to maintain satisfactory control on protamine zinc insulin alone. Insulin is not available long enough to furnish continued control from one daily injection. When it is taken twice a day, there have resulted periods of severe shock, with the extreme and erratic symptoms peculiar to the persisting hypoglycemia from protamine zinc insulin. These seem to result from the prolonged effect of this form of insulin, with overlapping periods during which excess insulin is active. A small number of the severely diabetic patients have been asked to take two daily injections of crystalline zinc insulin at a twelve hour interval. This has not given fully satisfactory control, but the results have been better than with precipitated insulin alone.

Unless injections of insulin are to be taken at least twice daily, patients with severe diabetes present the problem of finding the form of insulin that gives an adequate and even insulin supply for the period in the twenty-four hours that is not covered by insulin from the protamine zinc form. One morning dose of the slowly acting insulin, with regular

insulin taken morning and noon or morning and evening, has not given satisfactory and maintained control. While we are in full agreement that crystalline zinc insulin does not give the prolonged effect that is obtained with insulin derived from the protamine zinc preparation, we find that it is able to give protection for a few hours longer than can the amorphous insulin. This is particularly evident in cases of severe diabetes without complications that shorten the duration of effect of any available insulin. The more prolonged control (into the late afternoon) with a morning dose of crystalline zinc insulin together with control at night from protamine zinc insulin has given more satisfactory results (with a smaller unit requirement) than any routine we have tried.

All patients using insulin have been taught to make the injections into the subpannicular space. Patients in whom tender lumps or localized areas of redness have appeared at the site of injection have found that these will disappear with improvement in their technic of injection. Cutaneous tests for possible allergic sensitiveness have given negative results in every case with both protamine zinc and crystalline zinc insulins. Two patients had acute and severe spastic colitis within a few days after beginning to take protamine zinc insulin. The complication cleared when they returned to the amorphous insulin. Both had the same experience with crystalline zinc insulin. Cutaneous tests with zinc insulin combinations gave negative results. Both patients have moderately severe diabetes of acute onset, and both have been observed for twelve to fifteen years.

Four patients with moderately severe diabetes had been using crystalline zinc and protamine zinc insulins, taken each morning, for eight or more weeks. They were asked to change to the clear crystalline zinc form, with two injections daily. Several days after this change, these patients were found in severe insulin shock in the late hours of the night. The clinical picture and resistance of the condition was similar in each patient to hypoglycemia from the protamine zinc insulin, but there had been a period of three to ten days since any precipitated insulin had been taken. Patients who have had "insulin reaction" symptoms from the crystalline zinc form have had symptoms similar to those experienced with amorphous insulin, with rapid recovery. The possibility of incomplete absorption of insulin from the protamine zinc preparation, with late liberation of the "pocketed" insulin, could be a possible cause of the experience of the 4 patients.

Symptoms of "insulin reaction," with glycosuria and hyperglycemia, have been observed in past years with the amorphous insulin. These experiences were not frequent and were never severe. In the few years that zinc insulin combinations have been used, we have had several experiences with an extreme degree of this overcompensation with the

use of both forms of zinc insulin. Two patients, aged 11 and 67 years, both with moderately severe diabetes, were found deeply unconscious during the night. Both were noisy and wildly restless. The values for blood sugar were 368 and 400 mg. per hundred cubic centimeters respectively when the patients were first seen. The older patient received dextrose intravenously, as oral feeding was not possible at first. Oral feedings were then carried out with both patients for twelve and sixteen hours, totals of 50 and 65 Gm. of carbohydrate being given. Neither patient received any insulin, and both were fully conscious at the end of twelve and sixteen hours. The values for blood sugar were then found to be 16 and 42 mg. per hundred cubic centimeters respectively.

Physical exercise appears to play an important role in the effectiveness of insulin of the crystalline zinc form. This has been manifested during the last year in patients of school and college age both with crystalline zinc insulin alone and with crystalline zinc and protamine zinc insulin taken in morning injections. It has been found necessary to reduce the unit dose of the crystalline zinc form as much as 10 units on the days when the patients are more than normally active. During the summer vacation, when the patients are at the seashore or in the mountains and unusually active, the same reductions are necessary.

All crystalline zinc insulin used in routine therapy is the product of Eli Lilly & Co. or of Frederic Stearns & Company. That used in the studies reported here was supplied by Eli Lilly & Co.

Progress in Internal Medicine

INFECTIOUS DISEASES

A REVIEW OF SIGNIFICANT PUBLICATIONS IN 1939-1940

HOBART A. REIMANN, M.D.
PHILADELPHIA

CHEMOTHERAPY

This year again, as in 1939, judging by the number of papers published on the subject, interest in chemotherapy dominates the field of infectious diseases. It is said that the incredible amount of 187 tons of sulfanilamide was used in the United States last year. Controlled experiments, too numerous to mention here, have in general confirmed earlier opinion as to the effectiveness or ineffectiveness of the sulfonamide derivatives in many diseases; in regard to others uncertainty still exists. In a recent review [1] are listed and discussed numerous infections for which both practical and experimental studies in man and in animals have shown the drugs to be of value, of doubtful value and of no value. There have also been many papers with overly enthusiastic conclusions from observations in single cases or in an insufficient number of uncontrolled therapeutic tests. The Council on Pharmacy and Chemistry of the American Medical Association has issued a revision of previous statements about both sulfanilamide and sulfapyridine [2] (2-[paraaminobenzenesulfonamido]-pyridine).

The mode of action of sulfanilamide, a matter of great importance, is still unknown. Numerous theories have been expressed. Locke and Mellon [3] take exception to Shaffer's view of the ability of sulfanilamide to act as a reservoir for an intermediate substance of high oxidizing intensity, and to the claim that the toxic and the therapeutic effects have the same mechanism. The chemotherapeutic properties, they believe,

From the Department of Medicine, Jefferson Medical College and Hospital.

1. Kolmer, J. A.: Progress in Chemotherapy of Bacterial and Other Diseases, Arch. Int. Med. **65**:671-743 (April) 1940. Heubner, W.: Chemotherapie von Infektionskrankheiten, Klin. Wchnschr. **19**:265-269 (March 23); 289-293 (March 30) 1940.

2. Sulfanilamide and Sulfapyridine, New and Nonofficial Remedies, J. A. M. A. **114**:326-327 (Jan. 27) 1940.

3. Locke, A., and Mellon, R. R.: The Mode of Action of Sulfanilamide, Science **90**:231-232 (Sept. 8) 1939.

are to be sought in an active attack on the defense of the pathogen against peroxide, namely, against catalase, not on its defense against oxygen want. They postulate the stepwise formation of, first, a therapeutically active derivative and, second, a toxic derivative. Sulfanilamide, they reiterate, may produce only a retardation of the growth of pathogens susceptible to its action.

In another paper Mellon and McKinney,[4] dealing with the pneumococcus, suggest that the accumulation of hydrogen peroxide after sulfapyridine therapy induces a form of dissociation of this bacterium. This phasic dissociation is not of the usual "M, S, R" sequence but involves a dwarf and a "G" type of colony, which are engulfed by phagocytes and destroyed. Many previous studies, however, provide no evidence that recovery from infection depends on microbic dissociation.

Broh-Kahn [5] does not agree that sulfanilamide is bacteriostatic only in the presence of oxygen. His findings are like those of Bliss and Long,[6] who reported bacteriostasis occurring under anaerobic conditions as well. His experiments indicate that the mechanisms suggested by Locke and Shaffer are not the sole ones concerned.

Lockwood's [7] theory is of particular interest because of its simplicity. He suggests that sulfanilamide interferes with the ability of certain bacteria to utilize assimilable nitrogen in the form of protein split products in serum and other body fluids and that the presence of peptone provides assimilable nitrogen in such excess that the drug no longer acts effectively. It is possible that the drug combines in some way with free amino nitrogen and renders it unsuitable as food material for bacteria. Such a theory may explain the failure of the drug to cause bacteriostasis of certain micro-organisms in pus or in traumatized wounds.

New compounds are constantly being made and tested. One of them, sulfathiazole (2-[sulfanilamido]-thiazole), causes less nausea and vomiting but is as effective in pneumococcic pneumonia as sulfapyridine.[8] Another compound, sulfamethylthiazole (2-sulfanilamido-4-methylthiazole), was found to be more effective than others against the

4. Mellon, R. R., and McKinney, R. A.: The Biologic Nature of Sulfapyridine's Bacteriostatic Effect Against the Pneumococcus, Proc. Soc. Exper. Biol. & Med. **42**:677-679 (Dec.) 1939.

5. Broh-Kahn, R. H.: The Bacteriostatic Action of Sulfanilamide Under Anaerobic Conditions, Science **90**:543-544 (Dec. 8) 1939.

6. Bliss, E. A., and Long, P.: Observations upon the Mode of Action of Sulfanilamide and Sulfapyridine, abstracted, Report of the Proceedings of the third International Congress for Microbiology, New York, Sept. 2-9, 1939, New York, The Congress, 1940, pp. 585-586.

7. Lockwood, J. S., and Lynch, H. M.: Studies on the Mechanism of the Action of Sulfanilamide, J. A. M. A. **114**:937-940 (March 16) 1940.

8. Long, P. H.: Thiazole Derivatives of Sulfanilamide, J. A. M. A. **114**: 870-871 (March 9) 1940.

staphylococcus, especially in test tube experiments.[9] Clinical trials are not yet numerous enough for one to judge its practical value. In tissue culture studies Osgood [10] found neoarsphenamine in high dilution to be far more effective than sulfapyridine against a variety of gram-positive cocci.

Bauer and Rosenthal [11] show that the sulfur is apparently not essential to chemotherapeutic action. Compounds active against streptococci were made by substituting arsenic or phosphorus for sulfur.

Chemotherapy in Pneumonia.—Without critical thought, a glance at a recently published chart [12] of mortality from pneumonia, which shows a strikingly low death rate from pneumonia in 1938-1939 as compared with 1928-1929, might be taken to indicate a triumph of chemotherapy. If, however, similarly gathered statistics [13] of other recent years are examined, the "pneumonia death rate [was] at a record low" in 1937-1938. Beginning in August 1937, every month except two showed a lower mortality rate from pneumonia than did the same month in any other year since 1920. According to another statistical report by the United States Bureau of Census,[14] the mortality rate from "influenza and pneumonia" dropped from 207 per hundred thousand in 1900 to 114 per hundred thousand in 1937. The period covered by these statistics, of course, was before chemotherapy for pneumonia was available. The increasing use of serotherapy may have played a role, but hardly enough to account for so great a reduction in mortality. Before the important factors in lowering the death rate can be discovered it is necessary to know the morbidity rate of the disease. If the morbidity rate is stationary and the mortality rate reduced as much as stated, there is reason to acclaim the success of specific therapy. Accurate figures, unfortunately, are not available. A significant fact is that in one

9. Barlow, O. W., and Hamburger, E.: Specific Chemotherapy of Experimental Staphylococcus Infections with Thiazole Derivatives of Sulfanilamide, Proc. Soc. Exper. Biol. & Med. **42**:792-795 (Dec.) 1939.

10. Osgood, E. E.: Effectiveness of Neoarsphenamine, Sulfanilamide, Sulfapyridine in Marrow Cultures with Staphylococci and Alpha Streptococci, Proc. Soc. Exper. Biol. & Med. **42**:795-799 (Dec.) 1939.

11. Bauer, H., and Rosenthal, S. M.: Studies in Chemotherapy: XI. Antibacterial Action of Phosphorus Compounds; Preliminary Report, Pub. Health Rep. **54**:2093-2095 (Nov. 24) 1939. Rosenthal, S. M.: Experimental Chemotherapy with Sulfanilamide and Related Compounds, J. A. M. A. **113**:1710-1714 (Nov. 4) 1939.

12. Seasonal Incidence of Pneumonia Greatly Reduced, Statist. Bull. Metrop. Life Ins. Co. **21**:7-8 (Feb.) 1940.

13. Pneumonia Death Rate at Record Low, Statist. Bull. Metrop. Life Ins. Co. **19**:6-8 (Sept.) 1938.

14. Major Causes of Death, Increase in Life Expectancy and Population Changes in the United States, Pub. Health Rep. **54**:2054-2064 (Nov. 17) 1939.

study [15] it was found that a drop of 27 per cent in mortality occurred in the first quarter of 1940 as compared with the same period in 1939.

It is probable that numerous factors are at play. In the control of typhoid fever, for example, increased knowledge, specific vaccine, improved sanitation, improved diet, control of carriers and other measures all combined to reduce the incidence. Similar factors were operative against tuberculosis. The lowest death rates in history were recently recorded [15] for diarrheal diseases, appendicitis and puerperal conditions. Whether or not serotherapy and chemotherapy are alone responsible for the recent lowering of the death rate in pneumonia, or whether the prevalence of this disease, like that of other diseases, is cyclic, and the present low ebb is merely a phase, only the future can tell. Whatever the cause, there is no doubt that the widespread use of chemotherapy and serotherapy, owing in part to the activities of numerous organized attempts to control pneumonia, can be expected to contribute to the advantage gained.

Indications are suggestive that unknown factors may also be operative. For example, in the experience of Reimann and Stokes [16] with an infection of the respiratory tract in 1939, probably caused by a filtrable agent, pneumococci were surprisingly scarce. They were isolated from the sputum of only 8 of 100 patients. It is generally believed that from 35 to 50 per cent of normal persons carry pneumococci in the nasopharynx habitually, and mild infections of the respiratory tract supposedly increase this percentage. The paucity of pneumococci in our own recent experience [16] may indicate a temporary diminution in their numbers and prevalence in certain localities as a result of influences totally unknown.

Except for confirmation of early reports, not much new information has accumulated as to the value of sulfapyridine in pneumococcic pneumonia. A bibliography of 122 references may be found in Marriott's paper.[17] A good review is also found in a paper by Long and Wood.[18] The consensus favors the use of chemotherapy but not to the exclusion of specific serum therapy. Chemotherapy seems to lower the mortality

15. Mortality Experience of the First Three Months of 1940: Sharp Drop in Deaths from Pneumonia, Statist. Bull. Metrop. Life Ins. Co. **21**:8 (April) 1940.

16. Reimann, H. A., and Stokes, J., Jr.: An Epidemic Infection of the Respiratory Tract in 1938-1939: A Newly Recognized Entity, Tr. A. Am. Physicians **54**:123-127, 1939. Reimann, H. A., and Havens, W. P.: An Epidemic Disease of the Respiratory Tract, Arch. Int. Med. **65**:138-150 (Jan.) 1940.

17. Marriott, H. L.: Sulphapyridine (M. & B.) 693) and Pneumococcal Infections, Brit. M. J. **2**:944-947 (Nov. 11) 1939.

18. Long, P. H., and Wood, W. B.: Observations upon the Experimental and Clinical Use of Sulfapyridine: II. The Treatment of Pneumococcal Pnuemonia with Sulfapyridine, Ann. Int. Med. **13**:487-512 (Sept.) 1939.

rate in pneumococcic pneumonia to about 5.5 per cent, according to Marriott, who summarizes the collective results in 1,991 treated patients. On the other hand, surprisingly low mortality rates of 2.3 per cent and 4.4 per cent following serotherapy have been reported.[19] Dowling and Abernethy [20] record a mortality rate of 14 per cent among 70 serum-treated patients and a rate of 9.6 per cent among those treated with sulfapyridine but do not believe that it is possible to judge the relative merits of either form of treatment yet. Aside from these figures there is at present no evidence to prove the superiority of one form of treatment over the other.[21] Unless work to decide this question is carefully controlled, inaccurate conclusions may be drawn. For example, it is highly probable that serum, because of the trouble and expense of giving it, is administered only to patients who are severely ill, while sulfapyridine is certainly used more indiscriminately. If many patients who are "suspected" of having pneumonia or who suffer from a condition erroneously considered to be pneumonia are included in statistics as drug-treated patients, the mortality rate will indeed be low.

Few physicians in actual practice will continue to use serotherapy, with its complicated details and expense, in preference to the simpler method of giving a few pills if the latter will yield equally good or better results and if the number of hazards is about the same. Several authorities advise chemotherapy alone in the average case but include specific immune serum when (*a*) sulfapyridine has been given for eighteen to twenty-four hours without improvement, (*b*) the patient is over 40 years of age, (*c*) the patient is pregnant or in the early puerperium, (*d*) more than one lobe is involved, and (*e*) the blood culture is positive.

In numerous states, particularly in New York, Massachusetts and Illinois, excellent brochures on the treatment of pneumonia have been prepared for free distribution by committees for the control of pneumonia. Unfortunately in some of them, as well as in current comment [22] and in a query,[23] sulfapyridine therapy is recommended as soon as a diagnosis

19. Loughlin, E. H.; Bennett, R. H., and Spitz, S. H.: The Treatment of Types V, VII and VIII Pneumococcal Pneumonias with Rabbit Antipneumococcus Serum, New York State J. Med. **39**:1713-1721 (Sept. 15) 1939. Callomon, V. B.: Treatment of Pneumonia with Type Specific Rabbit Serum, Am. J. M. Sc. **198**:349-356 (Sept.) 1939.

20. Dowling, H. F., and Abernethy, T. J.: Treatment of Pneumococcic Pneumonia: Comparison of Results Obtained with Specific Serum and with Sulfapyridine, Am. J. M. Sc. **199**:55-62 (Jan.) 1940.

21. Comparative Value of Serum Therapy and Chemotherapy in Pneumococcic Pneumonia, editorial, J. A. M. A. **114**:662-663 (Feb. 24) 1940.

22. Treatment of Pneumonia, Current Comment, J. A. M. A. **113**:2324 (Dec. 23) 1939.

23. Sulfapyridine Contraindicated in Prophylaxis of Pneumonia, Queries and Minor Notes, J. A. M. A. **114**:1689 (April 27) 1940.

of pneumonia is made. This recommendation, I believe, is too broad; the application of this drug should be restricted to clinical lobar pneumonia, or better still to pneumonia caused by the pneumococcus or by the hemolytic streptococcus, and perhaps the staphylococcus. There are many forms of pneumonia for which the drugs available are of no value. Blake and Haviland,[24] and the discussers of their paper, point out the ineffectiveness of sulfapyridine in pneumonia not caused by the pneumococcus. Furthermore, according to Brown and his co-workers:[25]

> The range between adequate blood concentration [of sulfapyridine] and those which carry an unwarrantable risk of serious toxicity has been shown to be so narrow as to provide justification for a more conservative approach to the chemical treatment of pneumonia and to constitute a valid argument against the indiscriminate substitution of sulfapyridine for sulfanilamide in non-pneumococcic infections.

Except under unusual circumstances there is at present no logical basis for the use of the sulfonamide compounds as prophylactic against pneumonia in persons who have infections of the respiratory tract. If, as has been estimated, pneumonia develops in only 1 of every 1,000 persons with colds, the uselessness of small doses and the occasional toxic results of effective doses of the drugs now available do not justify the risk of drug poisoning.

I have repeatedly pointed out that chemotherapy must not be used indiscriminately for every patient who has fever and a few rales in the lung. The drugs now available have no beneficial effect on the influenza-like pulmonary disease of extremely low mortality which has been prevalent for several years. Nor are they indicated in pulmonary congestion or in mixed infections of the lungs in which pneumococci or hemolytic streptococci are not present, although they have apparently been of value in postoperative pneumonia.[26] I have recently seen a number of patients with sulfanilamide poisoning to whom the drug was given without previous attempt having been made to discover the cause of the pneumonia, which in each case was atypical. In such cases it often happens that if no beneficial effect is noted after a reasonable trial of the drug, instead of stopping its use, the physician gives more and more until poisoning results. It is just as important to know when not to use chemotherapy and when to stop using it, as it is to know

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24. Blake, F. G., and Haviland, J. W.: Sulfapyridine in Pneumococcal, Streptococcal and Staphylococcal Infections, Tr. A. Am. Physicians **54**:130-148, 1939.

25. Brown, W. H.; Thornton, W. B., and Wilson, J. S.: An Evaluation of the Clinical Toxicity of Sulfanilamide and Sulfapyridine, J. A. M. A. **114**:1605-1611 (April 27) 1940.

26. Hinshaw, H. C., and Moersch, H. J.: Sulfapyridine in Treatment of Pneumonia with Special Reference to Postoperative Pneumonia, Arch. Surg. **39**:275-281 (Aug.) 1939.

when to use it. Whitby [27] believes such drug poisoning to be a matter of misjudgment not so much as regards primary prescription of the drug but as regards stopping its use after a trial period of a few days has shown no clinical effect. It would be important to learn whether many patients who supposedly die of an infection do not actually die from drug poisoning.

In the treatment of pneumococcic pneumonia there is still some uncertainty as to the optimal level of sulfapyridine in the blood. Some [28] believe that frequent measurements of the level have limited value, since many patients improve with 2 mg. or less per hundred cubic centimeters of blood; others [29] believe that results are better if the level is kept at 6 mg. per hundred cubic centimeters or higher. In this case the newly introduced, more soluble sodium salt of sulfapyridine when injected intravenously seems to be of value in raising the level to the desired point more speedily.[30] The intravenous injection of this compound is recommended when for some reason oral medication is difficult or impossible and when it is difficult to obtain a satisfactory amount in the blood. Unfortunately, unpleasant side effects, such as nausea, may occur, as with oral therapy (Finland and his co-workers [31]).

There is also uncertainty as to the length of time sulfapyridine therapy should be kept up after apparent recovery from pneumonia. Christian [32] suggests stopping therapy as soon as the temperature drops, but Blake, Longcope, Blankenhorn and Cecil [32] keep it up for several days after recovery, or approximately until the seventh or eighth day after the onset of the disease.

During the past winter sulfathiazole was tested in the treatment of pneumonia.[32a] In our hands it was as effective as sulfapyridine and caused

27. Whitby, L. E. H.: The Use and Abuse of Chemotherapeutic Agents of the Sulphonamide Group, Practitioner **144**:1-4 (Jan.) 1940.

28. Pepper, D. S.; Flippin, H. F.; Schwartz, L., and Lockwood, J. S.: The Results of Sulfapyridine Therapy in Four Hundred Cases of Typical Pneumococcic Pneumonia, Am. J. M. Sc. **198**:22 (July) 1939.

29. Abernethy, R. J.; Dowling, H. F., and Hartman, C. R.: The Treatment of Lobar Pneumonia with Sulfapyridine and Sodium Sulfapyridine, with Observations upon Effective Blood Levels, Ann. Int. Med. **13**:1121-1137 (Jan.) 1940.

30. Gaisford, W. F.; Evans, G. M., and Whitelaw, W.: Parenteral Therapy with Sulphapyridine Soluble, Lancet **2**:69-71 (July 8) 1939.

31. Finland, M.; Lowell, F. C.; Spring, W. C., and Taylor, F. H. L.: Parenteral Sulfapyridine: The Intravenous Use of Sodium Sulfapyridine and a Report of Clinical and Laboratory Observations on the Use of a Glucose Sulfapyridine Solution, Ann. Int. Med. **13**:1105-1120 (Jan.) 1940.

32. Christian, H. A.; Longcope, W. T.; Blankenhorn, M. A., and Cecil, R. L., in discussion on Blake and Haviland.[24]

32a. Flippin, H. S.; Schwartz, L., and Rose, F. B.: The Comparative Effectiveness and Toxicity of Sulfathiazole and Sulfapyridine in Pneumococcic Pneumonia, Ann. Int. Med. **13**:2038-2049 (May) 1940.

less nausea and vomiting. Erythema appeared in a few cases. The sodium salt of this compound is also effective when given intravenously.

Favorable reports continue to appear about chemotherapy in pneumococcic meningitis. Hodes and his co-workers [33] had success in 8 of 17 patients with this infection. English observers record 2 unsuccessful results; the treatment failed in a patient with empyema,[34] and in another patient pneumococcic meningitis developed during treatment of pneumonia with sulfapyridine.[35]

Experimental Studies.—Spring, Lowell and Finland [36] grew pneumococci in various concentrations of sulfapyridine and serum with the following results: Growth of pneumococci usually occurred equally well up to four hours in mediums with and without sulfapyridine. After this time the drug was bacteriostatic and bactericidal. The degree of effect noted depended on the concentration of the drug and the number of pneumococci inoculated. Growth always occurred before sulfapyridine exerted its effect. The combination of small amounts of serum with sulfapyridine was even more effective in causing bacteriostasis than either agent used alone. The presence of the specific soluble capsular substance did not reduce the efficiency of the drug.

In a clinical study the same authors [37] again demonstrated the superiority of a combination of serum and drug over either used separately. The bactericidal effect of specific immune serum was much more rapidly exerted than the bacteriostatic effect of the drug. The results of Kneeland and Mulliken [38] indicate that in most patients with lobar pneumonia treated with sulfapyridine an excess of antibody does not appear. It seems that the action of the drug on the bacteria lessens the need for antibodies, which are therefore not produced, because the stimulus is lacking. The drug apparently supplements, at least to some degree, the immune mechanism.

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33. Hodes, H. L.; Gimbel, H. S., and Burnett, G. W.: Treatment of Pneumococcic Meningitis with Sulfapyridine and the Sodium Salt of Sulfapyridine, J. A. M. A. **113**:1614-1619 (Oct. 28) 1939.

34. Aitchison, J. D.: Pneumococcal Meningitis Complicating Pneumococcal Empyema Treated Unsuccessfully with M. & B. 693, Lancet **1**:1436 (June 24) 1939.

35. Dowds, J. H.: Pneumococcal Meningitis Developing During Treatment with M. & B. 693, Lancet **1**:1436-1437 (June 24) 1939.

36. Spring, W. C.; Lowell, F. C., and Finland, M.: Studies on the Action of Sulfapyridine on Pneumococci, J. Clin. Investigation **19**:163-178 (Jan.) 1940.

37. Finland, M.; Spring, W. C., and Lowell, F. C.: Immunological Studies on Patients with Pneumococcic Pneumonia Treated with Sulfapyridine, J. Clin. Investigation **19**:179-199 (Jan.) 1940.

38. Kneeland, Y., and Mulliken, B.: Antibody Formation in Cases of Lobar Pneumonia Treated with Sulfapyridine, J. Clin. Investigation **19**:307-312 (March) 1940.

The experience of others [39] in treating dogs experimentally infected with a strain of type I pneumococci is in accord with clinical reports of the curative property of sulfapyridine. The influence of the drug was evident even in far advanced disease, but, as in man, its effectiveness was limited in the presence of suppurative complications. The authors could not confirm the reports of certain investigators that pneumococci lose their capsules during therapy. Type-specific capsulated pneumococci were found in both blood and lung tissue.

In Streptococcic Infections.—Sulfanilamide, according to Hoyne, Wolf and Prim,[40] is the most effective means of treatment of erysipelas. The fatality rate among 162 treated patients was 2.4 per cent, the lowest in their experience. Rantz and Keefer [41] also write that the drug shortens the course of the infection if given within the first three days. Complications, however, were frequent, and recurrence and relapse occurred in spite of treatment.

Chemotherapy is not always successful against infections with the hemolytic streptococcus. In a boy whose blood contained 14.9 mg. of sulfanilamide while he was under treatment for otitis media caused by the hemolytic streptococcus, peritonitis developed, and later pneumonia with pericarditis.[42] Such incidents support the view that chemotherapy alone is not always sufficient to overcome infection; an immune response from the host may also be necessary. The presence of pus inhibits bacteriostasis.

Patients with the usual forms of sore throat caused by the hemolytic streptococcus should not be given sulfanilamide unless serious complications, such as severe cervical adenitis, sinusitis, mastoiditis or meningitis, develop. In a controlled study, Rhoads and Afremow [43] show that the drug did not reduce the severity of tonsillitis, shorten its course, reduce the incidence of complications or reduce the duration of the carrier state. Sulfanilamide failed to check epidemics of scarlet

39. Gregg, L. A.; Hamburger, M., and Loosli, C. G.: Sulfapyridine in Experimental Pneumococcic Pneumonia in the Dog, J. Clin. Investigation **19**:257-265 (Jan.) 1940.

40. Hoyne, A. L.; Wolf, A. A., and Prim, L.: Fatality Rates in the Treatment of Nine Hundred and Ninety-Eight Erysipelas Patients, J. A. M. A. **113**:2279-2281 (Dec. 23) 1939.

41. Rantz, L. A., and Keefer, C. S.: Sulfanilamide in the Treatment of Erysipelas, New England J. Med. **221**:809-813 (Nov. 23) 1939.

42. Botsford, T. W., and Lanman, T. H.: Primary Streptococcal Peritonitis: Report of a Case Which Developed While the Patient Was Undergoing Sulfanilamide Therapy, New England J. Med. **221**:651-653 (Oct. 26) 1939.

43. Rhoads, P. S., and Afremow, M. L.: Sulfanilamide in Treatment of Sore Throat Due to Hemolytic Streptococci, J. A. M. A. **114**:942-943 (March 16) 1940.

fever in an Australian hospital,[44] but small doses were given. Two children contracted scarlet fever associated with type II streptococci while under treatment.

One group of workers [45] report favorable results in the treatment of chronic ulcerative colitis. When one considers the unknown cause of the disease and the tendency toward spontaneous remission, the results seem unconvincing.

The British Royal Army Medical Corps [46] has issued a memorandum on the prophylaxis and treatment of war wounds likely to be infected with streptococci or gas-forming bacilli. Patients who have such wounds are to be given 4 Gm. of sulfanilamide at once, 2 Gm. four hours later, then 1 Gm. every four hours for ten days. Then if no benefit is apparent, sulfapyridine should be used. Subsequent studies [47] support the prophylactic use of drugs, but the authors recommend that 1.5 Gm. be given as soon as possible after the wound has been received, followed by doses of 0.5 Gm. each at four hour intervals for four days.

In Subacute Bacterial Endocarditis.—Two more cases of apparent recovery from endocarditis after treatment with sulfanilamide are reported,[48] but Spink and Crago [49] report that of 11 patients only 2 seemed to be temporarily helped, and 1 of these died later. Reasoning that drugs cannot attack bacteria when these are buried deep in clots or vegetations on the cardiac valves, other investigators [50] gave patients sulfanilamide and heparin. Heparin is supposed to prevent the formation of fibrin clots and leave the streptococci unprotected against the drug. In our own experience and in that of others (unpublished) the

44. Keogh, E. V.; McDonald, I.; Battle, J.; Simons, R. T., and Williams, S.: Some Factors Influencing the Spread of Scarlet Fever in an Institution, J. Hyg. **39**:664-673, 1939.

45. Brown, A. E.; Herrell, W. E., and Bargen, J. A.: Neoprontosil (Oral) in Treatment of Chronic Ulcerative Colitis, Ann. Int. Med. **13**:700-710 (Oct.) 1939.

46. The Chemotherapy of Infected War Wounds, Foreign Letters, J. A. M. A. **113**:1251 (Dec. 16) 1939.

47. Fuller, A. T., and James, G. V.: Dosage of Sulphanilamide in Prophylaxis of Wound Infections, Lancet **1**:487-490 (March 16) 1940.

48. Major, R. H., and Leger, L. H.: Recovery from Subacute Bacterial Endocarditis, J. Kansas M. Soc. **40**:324-325 (Aug.) 1939. Heyman, J.: Subacute Bacterial Endocarditis Successfully Treated with Sulfanilamide: Report of Well Established Case Eighteen Months After Recovery, J. A. M. A. **114**:2373-2375 (June 15) 1940.

49. Spink, W., and Crago, F. H.: Evaluation of Sulfanilamide in the Treatment of Patients with Subacute Bacterial Endocarditis, Arch. Int. Med. **64**:228-248 (Aug.) 1939.

50. Kelson, S. R., and White, P. D.: Treatment of Subacute Bacterial Endocarditis, J. A. M. A. **113**:1700-1702 (Nov. 4) 1939. Friedman, M.; Hamburger, W. W., and Katz, L. N.: Use of Heparin in Subacute Bacterial Endocarditis, ibid. **113**:1702-1703 (Nov. 4) 1939.

results of such treatment have been uniformly disappointing, especially in patients treated late in the disease. At the meeting of the American Society for Experimental Pathology in New Orleans, in March 1940, Gruhzit [51] announced a new drug, paranitrobenzoate, which protects mice against Streptococcus viridans. In my experience this bacterium was never pathogenic for mice, and one wonders what technic was used to permit therapeutic tests to be made. No reports have been published as yet on the use of the drug in human patients.

In Staphylococcic Infections.—Although Blake and Haviland [24] noted no benefit from sulfapyridine, others [52] have reported several cases of bacteremia in which the drug was used, often together with many other measures, and the patients recovered. Single case reports concerning relatively common infections may mislead one to be prematurely enthusiastic about chemotherapy and would better be withheld until more comprehensive studies have been made. Furthermore, many physicians still regard "staphylococcic septicemia as almost invariably fatal."[52a] Such is not the case; the mortality rate without special therapy is about 60 per cent, so that any procedure may be wrongly credited with a 40 per cent cure rate. The prognosis is even more favorable in the case of children, and 3 of the 4 instances reported concerned children. British writers are also guilty of publishing reports of uncontrolled studies or of single cases,[53] and in one study [54] only 2 of 6 patients recovered. Many competent observers, however, are enthusiastic about the results in certain cases.

Hope may be had, however, for better success since two new compounds sulfamethylthiazole (2-sulfanilamido-4-methylthiazole) and sulfaphenylthiazole (2-sulfanilamidophenylthiazole) have been found to be more effective than previously used drugs against staphylococci in broth cultures.[55] As might have been expected, a report [55b] has already

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51. Gruhzit, A. M.: A New Approach in the Therapy of Septicemia Due to Streptococcus Viridans in Experimental Animals, abstracted, Arch. Path. **29**:732 (May) 1940.

52. (*a*) Thornhill, W. A.; Swart, H. A., and Reel, C.: Sulfanilamide in Staphylococcic Septicemia, J. A. M. A. **113**:1638-1639 (Oct. 28) 1939. (*b*) Goldberg, S. L., and Sachs, A.: Sulfapyridine in the Treatment of Staphylococcus Aureus Bacteremia, ibid. **113**:1639-1641 (Oct. 28) 1939.

53. Galewski, S., and Stannus, H. S.: Septicemia Due to Staphylococcus Albus Treated with M. & B. 693, Lancet **2**:1067-1068 (Nov. 18) 1939.

54. Abramson, A. W., and Flacks, B.: Staphylococcal Septicaemia Complicating Carbuncle of the Face, Lancet **2**:1065-1067 (Nov. 18) 1939.

55. (*a*) Lawrence, C. A.: Bacteriostatic Actions of Three Thiazole Derivatives of Sulfanilamide upon Bacteria in Broth Cultures, Proc. Soc. Exper. Biol. & Med. **43**:92-97 (Jan.) 1940. (*b*) Herrell, W. E., and Brown, A. E.: The Clinical Use of Sulfamethylthiazol in Infections Caused by Staphylococcus Aureus: Preliminary Report, Proc. Staff Meet., Mayo Clin. **14**:753-758 (Nov. 29) 1939.

been published of a single case in which the drug supposedly had curative value. In one study [56] sulfathiazole was better than sulfamethylthiazole in experiments on mice, but the reverse was true in the test tube. The observers rightly point out how minor variations in the technic used can greatly influence the results. In another study [57] sulfathiazole was more effective than sulfapyridine. It may be of importance to use both drugs and specific immune serum [58] in combating staphylococcic infections.

In Peritonitis.—Surgeons report a marked reduction of mortality from peritonitis after appendectomy in patients treated with sulfanilamide.[59] The mortality rate among 552 patients before sulfanilamide was available was 1.5 per cent. In a subsequent group of 257 who were treated in the same way but received the drug in addition, the rate was 0.4 per cent. Unfortunately, alternate controls were not studied at the same time, a fact which considerably reduces the significance of this report. No special attempts were made, or recommended, toward discovering the causative bacteria.

In Gonococcic Infections.—Futcher and Scott [60] treated 4 patients for gonococcic endocarditis with sulfanilamide. Three died, and the diagnosis of the condition for the one who recovered was not fully proved.

Although sulfanilamide is regarded almost unanimously as the most effective treatment yet used in treating gonorrheal urethritis, relapses frequently occur. In one series of 1,005 patients at least 12 per cent had relapses.[61]

In Miscellaneous Conditions.—The effect of sulfanilamide in tuberculosis is still controversial. Experiences of Follis and Rich [62] with

56. Rake, G., and McKee, C. M.: Action of Sulfathiazole and Sulfamethylthiazole on Staphylococcus Aureus, Proc. Soc. Exper. Biol. & Med. **43**:561-564 (March) 1940.

57. Bliss, E. A., and Ott, E.: Effect of Sulfapyridine, Sulfathiazole and Sulfamethylthiazol upon Some Staphylococcic Infections in Mice, Proc. Soc. Exper. Biol. & Med. **43**:706-709 (April) 1940.

58. Julianelle, L. A.: Observations on the Specific Treatment (Type A Antiserum) of Staphylococcal Septicemia, Ann. Int. Med. **13**:308-316 (Aug.) 1939.

59. Ravdin, I. S.; Rhoads, J. E., and Lockwood, J. S.: The Use of Sulfanilamide in the Treatment of Peritonitis Associated with Appendicitis, Ann. Surg. **111**:53-63 (Jan.) 1940.

60. Futcher, P. H., and Scott, V. C.: Four Cases of Gonococcic Endocarditis Treated with Sulfanilamide with Recovery of One, Bull. Johns Hopkins Hosp. **65**:377-392 (Nov.) 1939.

61. Cokkinis, A. J., and McElligott, G. L. M.: Relapses After Sulfonamide Cure of Gonorrhea, Brit. M. J. **2**:1080-1083 (Dec. 2) 1939.

62. Follis, R. H., and Rich, A. R.: Further Studies on the Effect of Sulfanilamide on Experimental Tuberculosis, Bull. Johns Hopkins Hosp. **65**:466-483 (Dec.) 1939.

rabbits confirmed their previous observation that sulfanilamide in adequate doses and properly given has a definite inhibitory effect on the development of tuberculosis. Others [63] find that the drug has no effect on experimental tuberculous infection in guinea pigs. Sulfapyridine is slightly more effective than sulfanilamide in vitro, but sulfapyridine had no effect on tuberculosis in 7 patients.[64]

Sulfapyridine was more effective than sulfanilamide in the treatment of an infection with Friedländer's bacillus in mice, but too few animals were used in the experiments reported [65] to render final judgment possible as to the value of the drug. One patient with septicemia due to Friedländer's bacillus was given sulfapyridine and recovered.[66]

Too few mice were used to enable one to draw conclusions as to the effectiveness of sulfapyridine in experimental infection with Bacillus coli. An enthusiastic report of the beneficial effect of both sulfanilamide and sulfapyridine in the treatment of typhoid fever originated in England.[67] Seven patients were treated with apparently good results. Good results were also apparently attained in 3 of 4 other patients treated with sulfathiazole.[67a]

Success was reported [68] in treating an experimental infection with Listerella in mice. Sulfanilamide caused striking improvement in patients with chancroid.[69]

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63. Steinbach, M. M., and Dillon, B. M.: Sulfanilamide in Experimental Tuberculosis, Proc. Soc. Exper. Biol. & Med. **41**:613-616 (June) 1939. Birkhaug, K.: Sulphonamide Treatment of Experimental Tuberculosis in Guinea Pigs, Bergen, Norway, A. S. John Griegs Boktrykkeri, 1939; Bacteriostatic Effect of Sulfapyridine, Sulfanilamide and Prontosil Rubrum in Vitro on Mycobacteria, Proc. Soc. Exper. Biol. & Med. **42**:275-277 (Oct.) 1939.

64. Allison, S. T., and Myers, R: The Treatment of Pulmonary Tuberculosis with Sulfapyridine, J. A. M. A. **113**:1631-1634 (Oct. 28) 1939.

65. Kolmer, J. A., and Rule, A. M.: Sulfanilamide and Sulfapyridine in the Treatment of Experimental B. Friedländer (Klebsiella Pneumoniae) Infections of Mice, Proc. Soc. Exper. Biol. & Med. **42**:305-307 (Oct.) 1939.

66. Meyer, K. A., and Amtman, L.: Treatment of Friedlander's Septicemia by Sulfapyridine with Recovery, J. A. M. A. **113**:1641-1642 (Oct. 28) 1939.

67. Harries, E. H. R.; Swyer, R., and Thompson, N.: Sulfanilamide in Typhoid Fever, Lancet **1**:1321-1322 (June 10) 1939.

67a. Weilbaecher, J. O.; Moss, E. S.; Taylor, H. N., and Duprey, H.: The Treatment of Typhoid Fever by the Thiazole Derivatives of Sulfanilamide: A Preliminary Report of Four Cases, South. M. J. **33**:645-648 (June) 1940.

68. Porter, J. R., and Hale, W. H.: Effect of Sulfanilamide and Sulfapyridine on Experimental Infections with Listerella and Erysipelothrix in Mice, Proc. Soc. Exper. Biol. & Med. **42**:47-50 (Oct.) 1939.

69. Schwartz, W. F., and Freeman, H. E.: Sulfanilamide in Treatment of Chancroid, J. A. M. A. **114**:946-947 (March 16) 1940.

Sulfanilamide rendered 20 per cent of 77 patients with trachoma symptom free; 40 per cent were improved, and 40 per cent were unchanged.[70] Since the disease remained active, other supplementary measures seem to be needed.

Contrary to earlier favorable reports, sulfanilamide had no beneficial effect on experimental gas gangrene.[71] An antiserum for Clostridium welchii was effective in treatment.

Sulfapyridine protected mice against experimental infection with Haemophilus influenzae,[72] and clinical trial in a few patients with this infection has also given promise of success.[73] No benefit was observed in guinea pigs with Rocky Mountain spotted fever or with typhus,[74] or in mice infected with anthrax bacilli.[75]

In the accompanying table infections are grouped to show the relative effectiveness of chemotherapy for them. The chart emphasizes the necessity of etiologic diagnoses. Rearrangement of the list may be anticipated as knowledge increases and as new and more efficient drugs are made.

Effectiveness of Chemotherapy in Diseases

Curative in:	Of Doubtful Value in:	Of Little or No Value in:
Streptococcus haemolyticus infections (except in tonsillitis and in presence of pus)	Brucellosis	Purulent lesions with any bacteria
Pneumococcic pneumonia, septicemia, meningitis	Staphylococcic infections	Tuberculosis
Gonococcic urethritis, arthritis	Ulcerative endocarditis	Rickettsial diseases
Meningococcic meningitis	Ulcerative colitis	Almost all virus diseases
Colon bacillius infections of urinary tract	Scarlet fever	Streptococcus viridans endocarditis
	Typhoid fever	Rheumatic fever
	Clostridium welchii infections	Rheumatoid arthritis
	Friedländer's bacillus infections	Infectious mononucleosis
	Venereal lymphogranuloma	Malaria
	Trachoma	Fungous infections
	Plague	Spirochetal diseases
	Chancroid	Trichinosis
	Meningitis due to Pfeiffer's bacillus	Tularemia

70. Julianelle, L. A.; Lane, J. F., and Whitted, W. P.: Effect of Sulfanilamide on the Course of Trachoma, Am. J. Ophth. **22**:1244-1252 (Nov.) 1939.

71. Kendrick, D. B.: Treatment of Gas Gangrene Infections in Guinea Pigs with Neoprontosil, Sulfanilamide and Sulfapyridine: An Experimental Study, J. Clin. Investigation **18**:593-596 (Sept.) 1939.

72. Pittman, M.: The Protection of Mice Against Hemophilus Influenzae (Non-Type-Specific) with Sulfapyridine, Pub. Health Rep. **54**:1769-1775 (Sept.) 1939.

73. Roche, E. H., and Caughey, J. E.: Influenzal Meningitis Treated with M. & B. 693, Lancet **2**:635-638 (Sept. 16) 1939. Hamilton, T. R., and Neff, F. C.: Influenzal Meningitis with Bacteremia Treated with Sulfapyridine: Recovery, J. A. M. A. **113**:1123-1125 (Sept. 16) 1939.

74. Topping, N. H.: Experimental Rocky Mountain Spotted Fever and Endemic Typhus Treated with Prontosil or Sulfapyridine, Pub. Health Rep. **54**:1143-1147 (June 30) 1939.

75. Cruikshank, J. C.: Chemotherapy of Experimental Anthrax Infection, Lancet **1**:681-684 (Sept. 23) 1939.

PNEUMONIA

The chemotherapy of pneumonia is discussed on page 480.

Wood [76] recommends the use of the skin test with specific pneumococcus polysaccharide proposed by Francis as a guide to determine whether enough antipneumococcus serum has been injected. The test, it is claimed, when positive invariably denotes that recovery has begun; when negative, it indicates the need of further serum therapy. The test, Wood believes, is not used as widely as it should be, because many who have tried it did not apply it correctly or interpret its results properly. He presents evidence that the immediate wheal and erythema of the skin reaction are due to the local union of antibody and polysaccharide in the skin, perhaps in the nature of a local precipitin reaction, and indicate the presence of type-specific antibodies in the blood. Edwards and his associates [77] also believe the test to be valuable but not infallible.

In another paper Wood [78] points out the great variability in the amount of antibody required in the individual case of pneumococcic pneumonia. He deplores the adoption of routine injection of large amounts (100,000 or more units) of serum as wasteful, since all patients do not need so much. This seems to be especially true since the introduction of sulfapyridine. By the use of the Francis skin test it is possible to gage the amount of serum needed with considerable accuracy. No patient who failed to show a positive skin reaction recovered from pneumonia.

Hall [79] brings to attention an important hazard in obstetric practice, namely, that of aspiration pneumonitis. Unfortunately, only a few of the 15 examples of the condition he presents conform to the criteria of pneumonitis. In many, from the meager data given, it is impossible to give an opinion; in others, atelectasis or embolism may have occurred. There is no doubt, however, that vomiting or the development of a shocklike syndrome during parturition as a result of natural causes or from overmedication is a serious occurrence and ought to be guarded against more carefully. In reading over his case reports one is struck

76. Wood, W. B.: The Control of the Dosage of Antiserum in the Treatment of Pneumococcal Pneumonia: I. A Study of the Mechanism of the Skin Reaction to Type Specific Polysaccharide, J. Clin. Investigation **19**:95-104 (Jan.) 1940.

77. Edwards, J. C.; Hoaglund, C. L., and Thompson, L. D.: Type Specific Polysaccharide Skin Test in Serum Therapy of Pneumonia, J. A. M. A. **113**:1876-1880 (Nov. 18) 1939.

78. Wood, W. B.: The Control of the Dosage of Antiserum in the Treatment of Pneumococcal Pneumonia: II. The Clinical Application of the Francis Skin Test, J. Clin. Investigation **19**:105-121 (Jan.) 1940.

79. Hall, C. C.: Aspiration Pneumonitis: An Obstetric Hazard, J. A. M. A. **114**:728-733 (March 2) 1940.

by the number of drugs employed ante partum. In a fatal case the patient received sodium allyl, scopolamine hydrobromide, solution of posterior pituitary, morphine sulfate and gas anesthesia all within a period of four and one-half hours. It is not surprising that she vomited. Soon after delivery a shocklike condition was treated with atropine, oxygen–carbon dioxide, sucrose solution, metrazol and, later, transfusions of blood. Some of these, no doubt, are valuable remedies, but the variety used is reminiscent of the old days of polypharmacy, except that instead of being used all at once the drugs are applied in rapid succession. As a result, one may wonder, perhaps, not so much why untoward effects occur but why they do not occur oftener.

Oil Aspiration Pneumonia.—Several papers have appeared on this subject. Graef [80] stressed the pathologic features. He urges that intranasal medication with liquid petrolatum as a lubricant be stopped, because of the difficulty in expelling oil once it gets into the lung. Bishop [81] reviews 136 reported cases and gives a long list of references. To show the difficulty in arriving at a correct diagnosis of lipoid pneumonia, Thomas and Rienhoff [82] report a case in which pulmonary carcinoma was suspected. The patient was operated on and died; at necropsy aspiration of oil was found to have been the cause of the trouble. It was then learned that the patient had used an oil spray in his nose over a long period.

Chemical Pneumonia.—Considerable controversy, especially in Europe, exists over the nature of the so-called Thomas slag meal pneumonia.[83] Thomas slag is a by-product of certain methods of steel founding and is used as a fertilizer. It is a powdery substance containing, among other chemicals, phosphoric acid, calcium hydroxide, silicic acid and manganese dioxide. A high pneumonia rate has been noted among workers who handle the slag. Some believe the calcium hydroxide to be the irritant, others the manganese, but Gundel [84] minimizes the danger of these substances as a cause, since a similar incidence of pneumonia occurs among workers in other industries not associated with these

80. Graef, I.: Studies in Lipid Pneumonia: I. Lipid Pneumonia Due to Cod Liver Oil; II. Lipid Pneumonia Due to Liquid Petrolatum, Arch. Path. **28**:613-667 (Nov.) 1939.

81. Bishop, P. G. C.: Oil Aspiration Pneumonia and Pneumolipoidosis, Ann. Int. Med. **13**:1327-1359 (Feb.) 1940.

82. Thomas, H. M., and Rienhoff, W. F.: Lipoid Cell Pneumonia: Adult Type, South. M. J. **32**:1077-1080 (Nov.) 1939.

83. Kahlstorf, A.: Die Thomasschlackenmehlpneumonie, Deutsches Arch. f. klin. Med. **184**:466-483 (Aug. 1) 1939.

84. Gundel, M.: Pneumoniehäufungen in gewerblichen Betrieben, Bericht über den VIII. Internationalen Kongress für Unfallmedizin und Berufskrankheiten, Frankfurt, September 1938, Leipzig, Georg Thieme, 1939, pp. 1047-1054.

chemicals. His view is in line with that of American investigators, who emphasize the importance of overheating and chilling as to the pneumonia in steel mills. Gundel claims to have reduced the morbidity by specific vaccination with pneumococci of types I and II. Vaccines, however, were unsuccessful in Norway, where manganese in the smoke is believed to be responsible.[85]

Two more uncontrolled and unconvincing reports [86] have appeared concerning roentgen ray therapy in pneumonia. According to one author, the fact that the mortality rate (20 per cent) was the same in the patients treated with roentgen radiation as in those who had only a diagnostic roentgenogram made of the chest shows that even the roentgen rays used in making a plate of the chest (!) are beneficial in pneumonia. To test whether or not roentgen rays exert any influence in pneumococcic infections under controlled conditions, Havens and Casper [87] injected pneumococci intradermally in rabbits and treated them. The rays were ineffective in small doses, and when larger doses were used the mortality rate was greater in the treated than in the untreated animals.

Experiments with serum therapy by Kempf and Nungester [88] did not reveal any considerable penetration of specific antiserum into the alveoli of the lungs of infected rats. The blood is often rendered temporarily pneumococcus-free, but not the lungs. Perhaps some other mechanism, in addition, plays a role in recovery from pneumococcic infection. Further studies by Robertson and Van Sant [89] indicate that macrophages are more able to engulf and digest pneumococci than polymorphonuclear leukocytes and that macrophages from immunized animals are no more active than those from normal ones; both depend chiefly on opsonins for their activity.

Rich and McKee [90] also point to the leukocytes as factors of great importance in controlling infection. These observers show that rabbits

85. Manganese in Factory Smoke and Pneumonia in Sauda (Norway), Foreign Letters, J. A. M. A. **113**:1426 (Oct. 7) 1939.

86. Scott, W. R.: X-Ray Therapy in the Treatment of Acute Pneumonia, Radiology **33**:331-349 (Sept.) 1939. Solis-Cohen, L., and Levine, S.: Roentgen Treatment of Lobar Pneumonia, Am. J. Roentgenol. **42**:411-417 (Sept.) 1939.

87. Havens, W. P., and Casper, S.: Roentgen Ray Therapy in Pneumococcus Type I Infection in Rabbits, Proc. Soc. Exper. Biol. & Med. **42**:179-180 (Oct.) 1939.

88. Kempf, A. H., and Nungester, W. J.: Action of Antipneumococcus Serum in the Pneumonic Rat and Its Penetration into the Pulmonary Lesion, J. Infect. Dis. **65**:1-11 (July-Aug.) 1939.

89. Robertson, O. H., and Van Sant, H.: A Comparative Study of Phagocytes and Digestion of Pneumococci by Macrophages and Polymorphonuclear Leucocytes in Normal and Immune Dogs, J. Immunol. **37**:571-597 (Dec.) 1939.

90. Rich, A. R., and McKee, C. M.: The Pathogenicity of Avirulent Pneumococci for Animals Deprived of Leucocytes, Bull. Johns Hopkins Hosp. **64**:434-446, 1939.

deprived of their circulating leukocytes by the injection of benzene can be infected by "R" pneumococci, which are avirulent and promptly destroyed in normal animals. They believe that the ability of "R" pneumococci to become actively invasive and destructive is due chiefly, if not entirely, to the absence of circulating phagocytic cells. In this work and in that previously reported they seem to overlook the fact that in a rabbit severely poisoned with benzene many other changes take place besides a simple removal of leukocytes which may render animals susceptible to bacteria ordinarily avirulent in normal ones. They themselves question whether several animals did not die from benzene poisoning and not from the infection.

It seems to me that in many ideas concerning the prevention of and recovery from infections far too much importance has been attributed to the leukocytes. So much attention has been given to them, perhaps, because they can be easily studied both by enumeration and by histologic technics. They no doubt are important in the process, but many other factors are operative too.

STREPTOCOCCI

Boisvert [91] tested the reliability of the antifibrinolysin test for the diagnosis of recent infection with the hemolytic streptococcus. The test was at first believed to be specific, but it has been found to be positive in infections caused by other bacteria. In Boisvert's experience the test was strongly positive in many cases of pneumococcic pneumonia, but further study revealed that although the test was positive during the disease the positive reaction tended to diminish rapidly afterward, in contrast to the reactions in other infections, in which several reaction types or "trends" were noted during the disease. In some the test was never positive, in some it was persistent, in a few it was intermittently positive, and in others it was negative during the acute stage and positive later. The last trend was observed in most cases of infection with the hemolytic streptococcus, and in rheumatic fever the test was usually continuously high.

Antistreptolysin was present in 80 per cent of patients with scarlet fever and in the majority of patients with acute rheumatic fever and chorea.[92] It was absent as a rule in patients with rheumatoid arthritis despite the frequent presence of agglutinins for the same strain of streptococci used as antigen for the antistreptolysin test. The test was helpful in the diagnosis of atypical rheumatic fever, since it is seldom

91. Boisvert, P. L.: The Streptococcal Antifibrinolysin Test in Clinical Use, J. Clin. Investigation **19**:65-74 (Jan.) 1940.

92. Bunim, J. J., and McEwen, C.: The Antistreptolysin Test in Rheumatic Fever, Arthritis and Other Diseases, J. Clin. Investigation **19**:75-82 (Jan.) 1940.

positive in other forms of joint disease. Its presence in any disease does not necessarily prove that the hemolytic streptococcus is the cause. Some go so far as to say that the presence of agglutinins for streptococci in rheumatic fever does not any more indicate a causal relationship than the presence of agglutinins in rickettsial diseases (Weil-Felix reaction) indicates a causal relationship of Bacillus proteus to these diseases.

The first practical application of a preparation called gramicidin in the treatment of mastitis caused by Streptococcus agalactiae contagiosae in cows met with considerable success.[92a] Gramicidin is the alcohol-soluble, water-insoluble substance isolated by Dubos from cultures of a sporulating bacillus. It is bactericidal for numerous gram-positive bacteria.

INFLUENZA

Nelson and Oliphant [93] studied the pathologic aspects of infection caused by the virus of epidemic influenza in mice. In addition to the typical histologic changes in the mucous membranes of the respiratory tract and lungs as previously described by others, slight lesions were present in the liver, spleen, thymus and kidney, but none in the adrenal glands, brain, thyroid gland, heart, pancreas or gastrointestinal tract. In ferrets [93a] lesions were found only in the nose and lungs.

Straub [94] reports studies similar to those of Francis and Stuart-Harris in 1938 on the effects of the virus of epidemic influenza on the mucous membranes of the respiratory tract in rats. The virus specifically affects the epithelium from the bronchioles to the bifurcation of the trachea. It causes catarrhal bronchitis with collapse of lung tissue. The collapse itself is nonspecific and is merely a complication of the obstruction. Severe infection leaves metaplastic epithelial changes, which render mice temporarily immune to reinfection. Mild attacks which leave no changes in the mucous membranes give no immunity.

Another factor in immunity against the virus of epidemic influenza may reside in certain properties of the nasal secretion. Burnet and his

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92a. Little, R. B.; Dubos, R. J., and Hotchkiss, R. D.: Action of Gramicidin on Streptococci of Bovine Mastitis, Proc. Soc. Exper. Biol. & Med. **44**:444-445 (June) 1940.

93. Nelson, A. A., and Oliphant, J. W.: Histopathological Changes in Mice Inoculated with Influenza Virus, Pub. Health Rep. **54**:2044-2054 (Nov. 17) 1939.

93a. Perrin, T. L., and Oliphant, J. W.: Pathologic Histology of Experimental Virus Influenza in Ferrets, Pub. Health Rep. **55**:1077-1086 (June 14) 1940.

94. Straub, M.: The Histology of Catarrhal Influenzal Bronchitis and Collapse of the Lung in Mice Infected with Influenza Virus, J. Path. & Bact. **50**:31-36 (Jan.) 1940.

associates[95] report studies on a virus-inactivating agent in the nasal secretions of certain persons who could not be deliberately infected with the virus. In the test tube such nasal secretion acts more slowly on the virus than specific antibodies do and not at all in the cold. The nature of the inactivating agent is unknown. A similar agent was studied by Francis.[96]

The experience of Taylor and Dreguss[97] in Hungary failed to show the effectiveness of formaldehyde-inactivated influenza virus. Little difference was noted during an epidemic between those who were vaccinated and those who were not. However, since five different strains of virus were isolated, it is possible that vaccine prepared against one strain has no effect against another. The five strains isolated tended to form a group separate from WS, PR8 and swine influenza virus.[98] A new approach to the problem of vaccine for multiple strains of influenza virus is suggested by the observations of Horsfall and Lennette.[99] They made a vaccine from ferrets which had had both influenza and a subsequent incidental distemper-like disease. The vaccine, freshly prepared, served as a surprisingly efficient immunizing agent against several different strains of influenza virus and against the virus of dog distemper. Vaccines prepared from animals infected with either influenza virus or distemper virus alone were unsatisfactory, and, disappointingly, repeated attempts to make vaccines from animals which had had both influenza and distemper were seldom as successful as the vaccine of the original experiment.

During the outbreak in England in 1939 further attempts were made to test the value of anti-influenza vaccine.[100] The results were disappointing and inconclusive. Unfortunately, in spite of several pessimistic reports, commercial exploitation of "influenza virus vaccine" has already begun in England, where the sale of such uncertain

95. Burnet, F. M.; Lush, D., and Jackson, A. V.: A Virus-Inactivating Agent from Human Nasal Secretion, Brit. J. Exper. Path. **20**:377-385 (Oct.) 1939.

96. Francis, T.: The Inactivation of Epidemic Influenza Virus by Nasal Secretions of Human Individuals, Science **91**:198-199 (Feb. 23) 1940.

97. Taylor, R. M., and Dreguss, M.: An Experiment in Immunization Against Influenza with a Formaldehyde-Inactivated Virus, Am. J. Hyg. (Sect. B) **31**:31-35 (Jan.) 1940.

98. Taylor, R. M.; Dreguss, M., and DeRitis, F.: Antigenic Behavior of Certain Hungarian Strains of Epidemic Influenza Virus, Am. J. Hyg. (Sect. B) **31**: 36-45 (Jan.) 1940.

99. Horsfall, F. L., and Lennette, E. H.: A Complex Vaccine Effective Against Different Strains of Influenza Virus, Science **91**:492-494 (May 24) 1940.

100. Stuart-Harris, C. H.; Smith, W., and Andrewes, C. H.: The Influenza Epidemic of January-March 1939, Lancet **1**:205-211 (Feb. 3) 1940.

products is under less control than in the United States (see advertisement in *Lancet,* Feb. 3, 1940).

Taylor [101] was able to transfer infections from human patients directly to hamsters. Infections in these mouselike animals were proved by the development of specific antibodies against known strains of influenza.

Chapman and Hyde [102] isolated the virus of influenza from 6 of 9 patients in 1936-1937. They cultured the virus on the chorioallantoic membrane of the chick embryo and found this medium to be as sensitive as the ferret for primary isolation of the virus. They were not successful in isolating a virus from patients with the common cold.

Prevalent Influenza-like Disease.—Stokes, Havens and I [16] report studies on a widespread influenza-like epidemic infection of the respiratory tract in the winter of 1939. Fifty per cent of a group of 800 persons were ill, most of them (87 per cent) with a mild form of the disease, but 6 per cent were confined to bed with nasopharyngolaryngotracheobronchitis, and another 6 per cent had pneumonia in addition. Maxfield [103] experienced a similar outbreak in Texas and Murray [104] one in Massachusetts. Other observers also studied coincident epidemics and focused their attention chiefly on the severely sick patients, calling the disease various forms of pneumonia. This we believe to be misleading, since in our experience the patients with severe disease comprised only a small proportion (6 per cent) of all those involved by an otherwise mild infection. We suggest that until further studies reveal the etiologic agent, the entity be called "grip," in contrast to epidemic influenza, which is associated with a known filtrable virus. No success attended our efforts to isolate the causative agent in 1939.

Similar results are published by two British groups. Scattered epidemics in England, simultaneous with ours in the winter of 1939, were studied and compared with earlier epidemics of a clinically similar disease in which the virus of influenza seemed to be operative. For the most part, a clinical differentiation could not be made between cases in which the virus of influenza was involved and those in which it could not be detected. The authors [100] decided that each outbreak

101. Taylor, R. M.: Detection of Human Influenza Virus in Throat Washings by Immunity Response in Syrian Hamster (Cricetus Auratus), Proc. Soc. Exper. Biol. & Med. **43**:541-542 (March) 1940.

102. Chapman, J., and Hyde, R. R.: Antigenic Differences in Viruses from Cases of Influenza and Colds, Am. J. Hyg. (Sect. B) **31**:46-67 (Jan.) 1940.

103. Maxfield, J. R., Jr.: Atypical Pneumonia with Leucopenia, Texas State J. Med. **35**:340-345 (Sept.) 1939.

104. Murray, M. E., Jr.: Atypical Bronchopneumonia of Unknown Etiology, Possibly Due to a Filterable Virus, New England J. Med. **222**:565-573 (April) 1940.

consisted of a proportion of cases of infection with the virus of epidemic influenza mixed with many other cases of some clinically similar but etiologically different disease. Martin and Fairbrother's experience [105] indicated, as ours did in 1938, that an unknown virus may be the cause. They also isolated an elusive filtrable agent but were unable to prove its etiologic relation to the disease.

Except for a few differences, the clinical description of their cases closely matches ours. Sweating, an outstanding feature in our cases is, however, scarcely mentioned by the British group. This and certain other minor clinical differences may be actual, but since our patients were continuously under our observation during their illness, we feel that our observations were perhaps more detailed and more carefully recorded than those made by numerous persons in scattered epidemics.

Simultaneous with these epidemics of a disease of the respiratory tract of unknown origin, Horsfall and his collaborators [106] report 4 localized outbreaks of true epidemic influenza in New York, from which influenza virus was recovered. The height of the epidemics in mid-February coincided exactly with the one we report. Obviously, and as would be expected, two or more infections by different etiologic agents may occur in different places or in the same place at the same time. The clinical aspects of the two diseases are so similar in most cases that differentiation without special study is impossible. Similar to the previous experience of others, the New York investigators detected neutralizing antibodies against the virus of influenza in persons who had been in contact with patients with influenza but who had not been sick, suggesting that subclinical, symptomless infection had occurred in these persons.

Jennison and Edgerton [107] made interesting observations, using high speed photography on the expulsion of droplets of secretion during sneezing. They had in mind a study of droplet infection, which apparently plays so great a role in acute diseases of the respiratory tract. The droplets, they found, were so small and had so great a velocity as to cause rapid evaporation. The dry bacteria or viruses, if present, could then float about in the air as potential invaders of susceptible hosts.

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105. Martin, A. E., and Fairbrother, R. W.: An Epidemic of Apparent Influenza, Lancet **2**:1313-1315 (Dec. 23) 1939.

106. Horsfall, F. L.; Hahn, R. G., and Rickard, E. R.: Four Recent Influenza Epidemics: An Experimental Study, J. Clin. Investigation **19**:379-392 (March) 1940.

107. Jennison, M. W., and Edgerton, H. E.: Droplet Infection of Air: High Speed Photography of Droplet Production by Sneezing, Proc. Soc. Exper. Biol. & Med. **43**:455-458 (March) 1940.

RHEUMATIC FEVER

The observations of Stroud and Twaddle [108] lend more support to the plan for providing specialized institutional care for children with rheumatic heart disease. A number of such sanatoriums are scattered throughout the country, and it seems desirable to establish more of them to assist children to adjust themselves physically and emotionally to their handicap. The course of nearly 700 afflicted children was followed for fifteen years. Twenty-one per cent died. The greatest mortality occurred from three to five years after the first attack of rheumatic fever. Forty-eight per cent of the deaths occurred in the first six years. Of 27 girls who later became pregnant, congestive heart failure developed in only 1.

The characteristic signs of permanent valvular defects in one series [109] of 314 patients, if not present at the time of the original illness, appeared during the first decade in 25 per cent. The delayed appearance was usually associated with evidence of recurrence of rheumatic fever.

Jones [110] critically reviews the theories as to the cause of rheumatic fever in an impartial manner and concludes that the cause is as yet unknown. He refers to his interesting studies with Mote, presented at the Microbiologic Congress in New York in September 1939. A filtrable virus, not unlike that of influenza, was recovered from patients with rheumatic fever. It was apparently not found in normal persons, but the possibility that it may have been accidentally encountered in mice was not excluded. They do not suggest any etiologic relationship of the virus to the rheumatic fever.

Collis [111] in his review of bacteriologic studies of rheumatic fever still places much emphasis on the hemolytic streptococcus as a possible cause.

RHEUMATOID ARTHRITIS

Cobb, Bauer and Whiting [112] briefly review the difficulties involved in discovering the cause of rheumatoid arthritis. While evidence points to an underlying infection in most cases, many observers before the advent of bacteriology favored the neurogenic theory because of the

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108. Stroud, W. D., and Twaddle, P. H.: Fifteen Years Observation of Children with Rheumatic Heart Disease, J. A. M. A. **114**:629-634 (Feb. 24) 1940.

109. Bland, E. F., and Jones, T. D.: The Delayed Appearance of Heart Disease After Rheumatic Fever, J. A. M. A. **113**:1380-1383 (Oct. 7) 1940.

110. Jones, T. D.: The Etiology of Rheumatic Fever: A Discussion, J. Pediat. **15**:772-785 (Dec.) 1939.

111. Collis, W. R. F.: Bacteriology of Rheumatic Fever, Lancet **2**:817-820 (Oct. 14) 1939.

112. Cobb, S.; Bauer, W., and Whiting, I.: Environmental Factors in Rheumatoid Arthritis, J. A. M. A. **113**:608-670 (Aug. 19) 1939.

frequent symmetric distribution of the diseased joints. The authors bring forth more evidence to emphasize the importance of environmental stress, poverty, grief and family worries, which in certain instances seemed to be the only important inciting factors in the onset or exacerbations of rheumatoid arthritis. They recommend a more careful and detailed inquiry into the social and psychiatric events in all patients with the disease.

In another timely paper Margolis and Eisenstein [113] point out the uselessness of all supposedly specific therapeutic measures used in treating chronic arthritis. Sulfur, vaccines, fever therapy and sulfanilamide have all been disappointing. Gold salts show but little promise and may cause harmful side effects. The patients of Sidel and Abrams [114] responded just as satisfactorily to the subcutaneous injection of salt solution as to the intravenous injection of polyvalent streptococcus vaccine. The psychologic effect, they believe, seems more important than the substance injected. I may add that the percentage of patients improved in their report—72 and 68 per cent, respectively—is similar to what may be expected in the natural course of the disease without any treatment.

For a comprehensive review of the subject of rheumatic disease and its ramifications, the reader is referred to the sixth annual review of a special committee organized for this purpose.[115] Over a thousand titles are listed in the bibliography.

FOCAL INFECTION

Havens and I [116] gathered much of the pertinent material which has accumulated since Holman's paper in 1928 to support the case against the removal of teeth and tonsils in the hope of preventing or favorably influencing systemic disease. We show that the results of the practice over a period of twenty-five years do not justify it and conclude that (*a*) the theory of focal infection in the sense of the term used is unproved, (*b*) the infectious agents are unknown, (*c*) large groups of

113. Margolis, H. M., and Eisenstein, V. W.: Some Specific Measures in the Treatment of Rheumatoid Arthritis, J. A. M. A. **114**:1429-1434 (April 13) 1940.

114. Sidel, N., and Abrams, M. I.: Treatment of Chronic Arthritis: Results of Vaccine Therapy with Saline Injections Used as Controls, J. A. M. A. **114**:1740-1742 (May 4) 1940.

115. Hench, P. S.; Bauer, W.; Dawson, M. H.; Hall, F.; Holbrook, W. P.; Key, J. A., and McEwen, C.: The Problem of Rheumatism and Arthritis: Review of American and English Literature for 1938 (Sixth Rheumatism Review); Part I, Ann. Int. Med. **13**:1655-1739 (March) 1940; Part II, ibid. **13**:1837-1990 (April) 1940.

116. Reimann, H. A., and Havens, W. P.: Focal Infection and Systemic Disease: A Critical Appraisal; the Case Against Indiscriminate Removal of Teeth and Tonsils, J. A. M. A. **114**:1-6 (Jan. 6) 1940.

persons whose tonsils are present are no worse than those whose tonsils are out, (*d*) patients whose teeth and tonsils are removed usually continue to suffer from the ailment for which they were removed, (*e*) beneficial effects when they do occur can seldom be ascribed to surgical procedures alone, (*f*) beneficial effects which occasionally occur after surgical measures are often outweighed by harmful effects or by absence of any effect at all, and (*g*) many suggestive foci of infection heal after recovery from systemic disease, or when the general health is improved with hygienic and dietary measures. If an abscess or a chronic infection around a tooth is present with reasonable certainty or if the tonsils are actually infected and the infection gives rise to repeated attacks of sickness, surgical measures may be indicated in selected patients.

Since our review of the subject, other papers supporting our views have appeared. Brown found that 62.8 per cent of the psychiatric patients had what are usually called foci of infection, and yet were without the diseases usually associated with them.[116a] Grossman [117] concludes from the evidence he presents that the indiscriminate extraction of pulpless teeth is unwarranted. In one study [44] children with and without tonsils were equally susceptible to infection with hemolytic streptococci, but infection, once established, persisted longer in children with tonsils. Illingworth [118] concludes that tonsillectomy in childhood does not prevent or limit nephritis; the procedure may even predispose patients to nephritis or actually cause it. We feel, however, that he exaggerates the danger. Another case in which endocarditis followed extraction of teeth was reported,[119] and others [120] point out the needlessness of removing tonsils for certain allergic conditions in children. The authors refer to the report that 1,235,000 tonsillectomies are performed each year in the United States. It would seem that many of these operations were needlessly done, and a time has come to check this "slaughter of tonsils," as it has been called.

It is also surprising to learn that a certain authority [121] infers not only that extraction of teeth and tonsillectomy may be helpful in the treatment of diabetes but also that these procedures may prevent the

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116a. Brown, C. H.: Foci of Infection in Psychiatric Patients, Am. J. M. Sc. **199**:539-545 (April) 1940.

117. Grossman, L. I.: Present Status of the Pulpless Tooth, Ann. Int. Med. **13**:1805-1813 (April) 1940.

118. Illingworth, R. S.: Tonsillectomy and Nephritis of Childhood, Lancet **2**:1013-1016 (Nov. 11) 1939.

119. Palmer, H. D., and Kempf, M.: Streptococcus Viridans Bacteremia Following Extraction of Teeth, J. A. M. A. **113**:1788-1792 (Nov. 11) 1939.

120. Hansel, F. K., and Chang, C. S.: Relation of Allergy and Tonsillectomy in Children, Arch. Otolaryng. **31**:45 (Jan.) 1940.

121. Wilder, R. M.: Diseases of Metabolism, in Barr, D. P.: Modern Therapy in General Practice, Baltimore, Williams & Wilkins Company, 1940, p. 888.

development of diabetes in blood relatives of the patient! Sepsis, if proved, no doubt, may provoke the development of diabetes or intensify it, but we believe the statement that "the teeth and tonsils more frequently than other sites are likely to harbor infection" cannot be supported with proof. One may speculate, first, on the presence of "infection" in other parts of the body less accessible to examination and, second, whether or not suspected infection may not heal spontaneously once the diabetes is controlled. The uncritical attitude with which many of the operations for the removal of foci of infection are performed reflects no credit on many specialists in laryngology. Since publishing our critique we have received letters from two friends of the late Dr. Frank Billings who, they said, regretted ever having raised the question of focal infection after he saw the extremes to which the theory was carried.

As examples of the type of misleading and uncontrolled information which editors of medical journals occasionally accept are papers in which authors [122] recommend the extraction of teeth to prevent pulmonary hemorrhage in patients with tuberculosis and tonsillectomy for the treatment of granulocytopenia.

Chronic Appendicitis.—In a manner somewhat different from that of our attack on the question of focal infection, Alvarez [123] has inquired into the rationale of performing appendectomy for "chronic appendicitis." He was astonished to find that among a group of 255 patients who were operated on for this reason, only 25 had had pain and soreness in the right lower quadrant of the abdomen with indigestion. Many were obviously neurotic persons. Furthermore, only 2 of the group were cured. In contrast to this, of course, there were 130 patients who had had at least one or more previous attacks of what might have been appendicitis. Of these, 87 (67 per cent) were cured by appendectomy. Alvarez points out that a person who has never had an acute attack of appendicitis who submits to appendectomy has 1 chance in 100 of relief from his complaints; he has also the same chance of dying from the operation. True chronic appendicitis, he believes, is one of the rarest of intra-abdominal diseases.

It seems to me that if the number of unnecessary appendectomies and tonsillectomies were reduced, it would diminish to a large extent the cost of medical care, about which we read and hear so much.

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122. Sprague, C. H.: Hemorrhage in Pulmonary Tuberculosis: Dental Focal Infection as a Principal Cause, Northwest Med. **38**:475 (Dec.) 1939. Holsti, Ö.; Meurman, Y., and Virkkunen, M.: Tonsillectomy in Emergency Treatment of Angina Granulocytopenia States, Acta med. Scandinav. **103**:430 (March 8) 1940.

123. Alvarez, W. C.: Chronic Appendicitis, J. A. M. A. **114**:1301-1306 (April 6) 1940.

BACILLARY DISEASES

There was an outbreak of a severe form of dysentery caused by Shigella dysenteriae in Michigan.[124] Ten deaths occurred among 45 patients. The average age of the patients was 8, and the majority were among the poor. An epidemic of dysentery in a Connecticut hospital resulted from the use of ice contaminated by a carrier.[125]

Felsen [126] reports success in treating patients with severe dysentery by giving them blood from donors who had previously been vaccinated with dysentery bacilli, colon bacilli and enterococci.

Undulant Fever.—Parsons, Poston and Wise [127] isolated Brucella melitensis from the lymph nodes of 7 patients with Hodgkin's disease and from none of the lymph nodes of 50 controls. The serum from patients with Hodgkin's disease, however, failed to agglutinate brucellas. In another paper,[128] describing wider experience, it is stated that Brucella was cultivated from the lymph nodes of 10 of 19 patients with Hodgkin's disease but from only 1 of 67 controls. The inference from this work may be that Brucella is etiologically related to Hodgkin's disease. The authors claim to be unable to differentiate chronic brucellosis of the glandular type from Hodgkin's disease. It must be said, however, that it is unsafe to emphasize histopathologic changes as indicating etiologic relationships. Furthermore, there are many who still remember the controversies regarding the relationship of the tubercle bacillus and a diphtheroid bacillus to Hodgkin's disease. Much more work will have to be done before Brucella is suspected seriously as the etiologic agent. Information, as yet unpublished, from at least two other laboratories indicates that it was not possible to confirm the results of Parson and Poston.

Robinson and Evans [129] made a clinical survey in a county of North Carolina of 325 cases in which patients suffered from chronic ill health, usually with low grade fever, psychoneurosis and unexplained abortions. In 22 of these cases the illness was diagnosed as chronic brucellosis. The authors show that in diagnosis too much reliance is often placed on the

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124. Block, N. B., and Ferguson, W.: An Outbreak of Shiga Dysentery in Michigan, 1938, Am. J. Pub. Health **30**:43-52 (Jan.) 1940.

125. Godfrey, E. J., and Pond, M. A.: A Hospital Epidemic of Flexner Dysentery Caused by Contaminated Ice, J. A. M. A. **114**:1151-1154 (March 30) 1940.

126. Felsen, J.: Clinical Notes on the Use of Immunized Donors in Chronic Bacillary Dysentery, Am. J. Digest. Dis. **7**:81-89 (Feb.) 1940.

127. Parsons, P. B.; Poston, M. A., and Wise, B.: The Pathology of Human Brucellosis, Am. J. Path. **15**:634-635 (Sept.) 1939.

128. Poston, M. A., and Parsons, P. B.: Isolation of Brucella from Lymph Nodes, J. Infect. Dis. **66**:86-90 (Jan.-Feb.) 1940.

129. Robinson, F. H., and Evans, A. C.: Chronic Brucellosis in Charlotte, North Carolina, J. A. M. A. **113**:201-207 (July 15) 1939.

agglutination test, the skin test or the opsonocytophagic test, the last being the least trustworthy. The best test, of course, is the isolation of the causative organism; this was isolated in 5 instances. The authors outline the clinical characteristics of the chronic form of the disease but overemphasize, it seems to me, the difficulties in diagnosis. In my experience undulant fever in its more acute form is not difficult to recognize. Like other infections, such as typhoid fever and tuberculosis, certain low grade or chronic forms may be confusing, but once the condition is in mind, appropriate observations and tests usually solve the problem.

A report of the water-borne outbreak among students in a bacteriologic laboratory was made.[130] Thirty-one per cent of 210 exposed students contracted the disease. Frank illness developed in 37 students and the latent form in 28. Fifteen other persons who had been in the building were infected. It was found that faulty plumbing by which sewage entered the water supply was the probable cause of the epidemic. The nature of the accident recalls the experience in Chicago with amebic dysentery several years ago.

Attempts are constantly under way to make an effective antiserum for brucellosis.[131] The results at present are unimpressive.

Tetanus.—Although 9 specific serologic types of Clostridium tetani are known, Maclennan [132] adds another and believes that many more exist. Nontoxigenic strains, he says, are comparatively common. In Gold's [133] experience with immunization against tetanus, two injections of alum-precipitated toxin produced a higher titer of antitoxin than three injections of plain toxoid. After the first injection the titer diminishes rapidly, necessitating reinjection. One week later the antitoxin titer may be from two to fifty times higher than that following the injection of 1,500 units of tetanus antitoxin. In some immunized persons the titer sixteen months later was well above the minimal protective level.

Tularemia.—Since Foshay's review [134] of tularemia appeared, it has been learned that infection occurs naturally in the beaver,[135] and the

130. Newitt, A. W.; Koppa, T. M., and Gudakunst, D. W.: Water-Borne Outbreak of Brucella Melitensis Infection, Am. J. Pub. Health **29**:739-743 (July) 1939.

131. Huddleson, I. F., and Pennell, R. B.: The Preparation and Purification of Brucella Antiserum, Science **90**:572-573 (Dec. 15) 1939.

132. Maclennan, J. D.: The Serological Identification of Cl. Tetani, Brit. J. Exper. Path. **20**:371-376 (Oct.) 1939.

133. Gold, H.: Active Immunization Against Tetanus, Ann. Int. Med. **13**:768-782 (Nov.) 1939.

134. Foshay, L.: Tularemia: A Summary of Certain Aspects of the Disease Including Methods for Early Diagnosis and the Results of Serum Treatment in Six Hundred Cases, Medicine **19**:1-83 (Feb.) 1940.

135. Scott, J. W.: Natural Occurrence of Tularemia in Beaver and Its Transmission to Man, Science **91**:263-264 (March 15) 1940.

bacillus has been found in the water of three streams in Montana by members of the United States Public Health Service.[136]

In spite of the favorable results reported by Foshay after the treatment of tularemia with specific immune serum, it is disappointing to read in an authoritative article[136a] that "there is no specific preventive or curative treatment for the disease."

Plague.—Eskey and Haas, and Hampton[137] again infer that plague infection among wild rodents is spreading eastward from the Pacific states. I have always doubted that this was the case. Since plague was first discovered in San Francisco in 1900, the disease, or one similar to it, has been found among rodents in many western states. This does not necessarily prove that the disease originated from the human patients or that it is spreading but may indicate that if one looks carefully enough one will find it in likely places. There is evidence that plague among wild rodents (sylvatic plague) is somewhat different from the classic bubonic plague carried by rats, but whether the sylvatic form has been modified from the human strain by passage through wild rodents, or whether it is a genuinely different variety, probably endemic on this continent, is impossible to state at present.

DISEASES CAUSED BY FILTRABLE VIRUSES

The latest advances in the knowledge of virus diseases were discussed at two important meetings during the past year. One was a symposium at Harvard Medical School in June 1939 and the other the Third International Congress for Microbiology at New York last September. The papers presented at both meetings are printed in book form[138] and should be available to those interested in the subject.

The invention of a new type of electronic microscope, differing in principle from any of those now in use and capable of magnifying particles from 25,000 to 30,000 times, was announced at the RCA Electronic Research Laboratories.[138a] A magnification of 5,000 was the high-

136. Tularaemia Infection Found in Streams, Pub. Health Rep. **55**:227 (Feb. 9) 1940.

136a. Sources, Symptoms and Prevention of Tularemia, Pub. Health Rep. **55**: 667-670 (April 19) 1940.

137. Eskey, C. R., and Haas, V. H.: Plague in the Western Part of the United States, Pub. Health Rep. **54**:1467-1481 (Aug. 11) 1939. Hampton, B. C.: Plague in the United States, ibid. **55**:1143-1158 (June 28) 1940.

138. Harvard School of Public Health, Symposium: Virus and Rickettsial Diseases with Especial Consideration of Their Public Health Significance, Cambridge, Mass., Harvard University Press, 1940. Report of the Proceedings of the Third International Congress for Microbiology, New York, Sept. 2-9, 1939, New York, The Congress, 1940.

138a. Zworykin, Y. K.: An Electron Microscope for the Research Laboratory, Science **92**:51-53 (July 19) 1940.

est heretofore possible with the ultraviolet ray optical microscope. It is possible that the new instrument will be helpful in further researches on the filtrable viruses and other infectious agents.

Encephalitis.—Equine encephalitis, according to Jakmauh and Feemster,[139] except for a higher mortality rate, is clinically so similar to other forms of acute infectious encephalitis that without special methods an etiologic diagnosis cannot be made. An accurate diagnosis should, of course, be made in every case, and for this purpose 10 cc. of blood should be withdrawn from the patient as soon as encephalitis is suspected and should be sent to a laboratory equipped to detect specific neutralizing antibodies. The virus is not present in the spinal fluid after the onset of symptoms, but is present in the brain, so that in fatal cases brain tissue may be removed at necropsy, placed in 50 per cent solution of glycerin and sent to a laboratory, where the virus may be isolated from animals inoculated with the material.

Investigators in North Dakota [140] observed the necessary precautions in establishing a correct diagnosis and reported an epidemic of 23 cases of equine encephalitis, which resembled the St. Louis type of encephalitis clinically yet differed in certain pathologic respects. Serum from only 1 of the 6 patients who recovered contained antibodies for the St. Louis type of virus, and serum from 4 patients neutralized the virus of western equine encephalitis. Similar diagnostic difficulties arose in California, where Howitt [141] made her studies. Forty deaths were recorded from encephalitis in the summer of 1937. In 1938 more cases developed. The virus of western equine encephalitis was isolated from 2 patients, but the serum of nearly one half of 103 patients tested contained neutralizing antibodies for the St. Louis type of virus. It appears that both kinds of encephalitis were present. They were frequently mistaken for poliomyelitis. It seemed that equine encephalitis affected a younger age group and probably originated locally; the St. Louis type affected older patients and was probably imported by migrant laborers.

A detailed clinical and pathologic report [142] of 8 cases in Boston in 1938 has been published. Here too the disease resembled the St. Louis

139. Jakmauh, P. H., and Feemster, R. T.: Laboratory Diagnosis of Encephalitis Due to the Equine Virus, New England J. Med. **221**:653-655 (Oct. 26) 1939.

140. Breslich, P. J.; Rowe, P. H., and Lehman, W. L.: Epidemic Encephalitis in North Dakota, J. A. M. A. **113**:1722-1724 (Nov. 4) 1939.

141. Howitt, B. F.: Viruses of Equine and of St. Louis Encephalitis in Relationship to Human Infections in California, 1937-1938, Am. J. Pub. Health **29**: 1083-1097 (Oct.) 1939.

142. Farber, S.; Hill, A.; Connerly, M. L., and Dingle, J. H.: Encephalitis in Infants and Children Caused by the Virus of the Eastern Variety of Equine Encephalitis, J. A. M. A. **114**:1725-1731 (May 4) 1940.

type of encephalitis in many respects. Serious neurologic disorders remained in 3 patients who survived.

An epidemic likely to have been one of equine encephalitis occurred in Iowa,[143] but since no specific tests were made, the diagnosis cannot be accepted. The presumptive clinical diagnoses were based on the clinical characteristics of the disease and on exposure to the disease in horses.

A laboratory employee who was working with the virus in a large, well equipped commercial laboratory contracted equine encephalitis and died.[144] The mode of infection is unknown. A vaccine like the one prepared by Beard and Finkelstein [145] may prevent such accidents. The latter vaccine, made from formaldehydized chick embryos and injected in doses of 1 cc., gave a satisfactory antibody response within a week. The constitutional reactions were often unpleasant. Vaccination is recommended for persons who are frequently exposed to the infection.

Lymphocytic Choriomeningitis.—Experiences in England further illustrate diagnostic difficulties in recognizing the various kinds of encephalitis. MacCallum and Findlay [146] isolated the virus of lymphocytic choriomeningitis from the cerebrospinal fluid and the nasopharyngeal washings of several patients suspected of having acute anterior poliomyelitis. There was no evidence of the presence of the virus of poliomyelitis. Moreover, these authors, together with Scott,[147] also isolated two strains of virus from human beings with a disease resembling lymphocytic choriomeningitis, but the strains were different from any other known viruses. The clinical picture was similar to that of the usual form of the disease, but no cross immunity was evident from tests in animals. In "size" also, as measured by filtration through membranes, the virus differed from typical strains.

In other experimental studies on guinea pigs the virus of lymphocytic choriomeningitis seemed to be able to penetrate the unbroken skin and cause infection.[148] This fact may be of important epidemiologic

143. Larimer, R. N., and Wiesser, E. G.: Human Equine Encephalitis, J. Iowa M. Soc. **29**:287-288 (July) 1939.

144. Fothergill, L. D.; Holden, M., and Wyckoff, R. W. G.: Western Equine Encephalomyelitis in a Laboratory Worker, J. A. M. A. **113**:206-207 (July 15) 1939.

145. Beard, J. W., and Finkelstein, H.: Vaccination of Man Against Virus of Equine Encephalomyelitis (Eastern and Western Strains), J. Immunol. **38**:117-136 (Feb.) 1940.

146. MacCallum, F. O., and Findlay, G. M.: Lymphocytic Choriomeningitis: Isolation of the Virus from the Nasopharynx, Lancet **1**:1370-1373 (June 17) 1939.

147. MacCallum, F. O.; Findlay, G. M., and Scott, T. M.: Pseudo-Lymphocytic Choriomeningitis, Brit. J. Exper. Path. **20**:260-269 (June) 1939.

148. Shaughnessy, H. J., and Zichis, J.: Infection of Guinea Pigs by Application of Virus of Lymphocytic Choriomeningitis to Their Normal Skins, Proc. Soc. Exper. Biol. & Med. **42**:755-757 (Dec.) 1939.

significance. More evidence is presented that house mice serve as a reservoir for the infection.[148a]

Herpes Simplex.—Anderson [149] published further evidence of the modification of the tropism of a filtrable virus by artificial means. A neurotropic strain of the virus of herpes simplex was changed by growth in chick embryos so that it no longer caused keratitis and encephalitis in rabbits but attacked the viscera instead. She has not yet determined whether the induced change of tropism or "mutation" is permanent or not.

Warren, Carpenter and Boak [150] note the frequency with which herpes simplex develops after a therapeutic induction of fever. During one period in 1933 extensive symptomatic herpes and mild symptoms of meningoencephalitis developed in each of 15 treated patients. Since 1936 the syndrome has appeared in only a few patients. In general, 42 per cent of all patients observed after fever treatment have had herpes. A much smaller number, 7 per cent, have had herpes after subsequent fever treatments, suggesting the establishment of immunity. The authors assume that the elevation of temperature provided the stimulus for the activity of the virus, which is usually present in a latent state in the patient. It seems likely that the virus is present not only in the saliva but in other secretions, and in tissues as well.

Findlay and MacCallum [151] describe a case of "traumatic" herpes, in which herpes developed at the site of an injury on a child's finger. Herpes, they believe, may be implanted on the skin, especially with saliva. Relapses often occur in spite of the presence of immune bodies. The site of residence of the virus during the latent period is unknown.

Poliomyelitis.—The manner of transmission of poliomyelitis is a subject of much controversy. Three routes are under investigation, the nasal pathway, the gastrointestinal route, and the cutaneous route associated with infection by mosquitoes. Some observers [152] believe it more logical at present to regard poliomyelitis as an intestinal disease than as

148a. Armstrong, C.; Wallace, J. J., and Ross, L.: Lymphocytic Choriomeningitis: Gray Mice, Mus Musculus, a Reservoir for the Infection, Pub. Health Rep. **55**:1222-1229 (July 5) 1940.

149. Anderson, K.: The Encephalitogenic Property of Herpes Virus, Science **90**:497 (Nov. 24) 1939.

150. Warren, S. L.; Carpenter, C. M., and Boak, R. A.: Symptomatic Herpes: A Sequela of Artificially Induced Fever, J. Exper. Med. **71**:155-168 (Feb.) 1940.

151. Findlay, G. M., and MacCallum, F. O.: Recurrent Traumatic Herpes, Lancet **1**:259-261 (Feb. 10) 1940.

152. Paul, J. R.; Trask, J. D., and Vignec, A. J.: New Aspects of the Clinical Epidemiology of Poliomyelitis, Tr. A. Am. Physicians **54**:119-122, 1939.

one entering through the respiratory tract. King [153] points out that the strains of virus are variable and that actually little is known about the interaction between virus and nerve tissue. In experimental studies, viruses which enter by the olfactory route seem to have a special ability to do so. Strains freshly isolated may be infective when inoculated subcutaneously, but this property is readily lost on aging. There is little evidence in the naturally occurring disease that the virus passes directly from the nasal mucous membrane by way of the olfactory neurons to the brain. In replying to the discussion of his paper, King [153a] states that a purely neurotropic virus is probably nonexistent. Most virus infections are systemic diseases, and the involvement of the nervous system may be the predominant feature or only a minor one. Both he and Sabin [154] discuss the problems of the local and constitutional barriers against infection of the nervous system by filtrable viruses. Sabin [154a] suggests that the presence or absence of certain factors either in the maternal diet during the nursing period or in the diet of actively growing young mice can promote, retard or inhibit the development of at least one type of constitutional barrier.

Paul, Trask and Culotta [155] demonstrated the presence of the virus of poliomyelitis in appreciable quantities in sewage from a city during an epidemic. These studies, in addition to previous ones [156] in which the virus was isolated from feces of patients and healthy contacts, and a subsequent one [157] in which statistical evidence pointed to a predominance of the disease in communities without adequate sewage disposal, add great weight to the theory that poliomyelitis enters and leaves the body through the gastrointestinal tract. It has also been suggested that the virus may enter through the nasal passages on bathing in water polluted with sewage.[158] Chlorine in a concentration of 0.5 part per million,

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153. King, L. S.: Some Problems in the Pathology of Neurotropic Viruses, J. A. M. A. **113**:1940-1945.

153a. King,[153] p. 1946.

154. Sabin, A. B.: Constitutional Barriers to Involvement of the Nervous System by Certain Viruses, Science **91**:84-87 (Jan. 26) 1940.

154a. Sabin, A. B.: Nutrition as a Factor in the Development of Constitutional Barriers to the Involvement of the Nervous System by Certain Viruses, Science **91**:552-554 (June 7) 1940.

155. Paul, J. R.; Trask, J. D., and Culotta, C. S.: Poliomyelitis Virus in Sewage, Science **90**:258-259 (Sept. 15) 1939.

156. Kramer, S. D.; Gilliam, A. G., and Molner, J. G.: Recovery of Virus of Poliomyelitis from Stools of Healthy Contacts in an Institutional Outbreak, Pub. Health Rep. **54**:1914-1922 (Oct. 27) 1939.

157. Casey, A. E., and Aymond, B. J.: The Distribution of Poliomyelitis in Louisiana, Science **91**:17-18 (Jan. 5) 1940.

158. Ellsworth, S. M.: Can Infantile Paralysis Be Spread by Bathing in Sewage-Polluted Water? New England J. Med. **222**:52-58 (Jan. 11) 1940.

which is greater than the concentration usually attained in municipal water purification, did not inactivate the virus of poliomyelitis.[158a]

Previous suggestions incriminating the mosquito as a vector of poliomyelitis receive no support from the work of Cornell and Davis,[159] who were unable to demonstrate the virus in mosquitoes which fed on a monkey suffering from the disease. That air currents or mosquitoes may be a factor in the spread of poliomyelitis is suggested by Murphy [160] from a geographic study of the peculiar distribution of cases in Nebraska. But a Canadian observer [161] encountered 4 cases, said to be instances of poliomyelitis, in November and in January 1939, which would seem not to support the theory of an insect vector unless one also introduces the possibility of long latency of infection after inoculation.

An important contribution to the experimental study of poliomyelitis was made by Armstrong,[162] who successfully established a strain of virus in the eastern cotton rat and subsequently in white mice. Whether this strain of virus alone or all strains are pathogenic for these conveniently handled animals is as yet unknown.

Rabies.—A great amount of interest has been revived in the study of rabies. An answer to a query [163] in *The Journal of the American Medical Association* advised against cauterization of wounds as an antiquated preventive measure; washing with soap and water and irrigation were said to suffice unless the wound was deep or irregular; in the latter case the wound should be opened or enlarged, to insure thorough cleansing, after which, if indicated, Pasteur's method of treatment should be instituted. Two physicians [164] take exception to the advice against cauterization of the wound and are answered by the Editor, who supports the advice given by referring to experiments which show how rapidly particulate matter is carried away from soft tissues by lymph. If this is

158a. Kempf, J. E., and Soule, M. H.: Effect of Chlorination of City Water on Virus of Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **44**:431-434 (June) 1940.

159. Cornell, V. H., and Davis, W. A.: Mosquito Transmission Experiment with Poliomyelitis Virus, Proc. Soc. Exper. Biol. & Med. **42**:78-80 (Oct.) 1939.

160. Murphy, J. H.: Comparative Epidemiology of Encephalomyelitis and Poliomyelitis, Nebraska M. J. **24**:453-458 (Dec.) 1939.

161. McGugan, A. C.: Outbreak of Acute Anterior Poliomyelitis in Alberta During the Winter Season, Canad. Pub. Health J. **30**:495-499 (Oct.) 1939.

162. Armstrong, C.: Experimental Transmission of Poliomyelitis to the Eastern Cotton Rat, Sigmodon Hispidus Hispidus, Pub. Health Rep. **54**:1719-1721 (Sept. 22) 1939; Successful Transfer of the Lansing Strain of Poliomyelitis Virus from the Cotton Rat to the White Mouse, ibid. **54**:2302-2305 (Dec. 29) 1939.

163. Dog Bites and Rabies, Queries and Minor Notes, J. A. M. A. **112**:1283 (April 1) 1939.

164. Dog Bites and Rabies, Queries and Minor Notes, J. A. M. A. **113**:1434 (Oct. 7) 1939.

the case with rabies virus, which it most likely is, there is no justification for the deliberate destruction of tissue with escharotics in the vain hope of preventing the spread of the infection, even after only a few minutes have elapsed since the virus was inoculated. Gloyne,[165] Kellogg [166] and Denison and Dowling [167] strongly support the use of nitric acid to cauterize the wound. The question obviously is unsettled.

Denison and Dowling [167] in a carefully prepared paper describe their experiences in Birmingham, Ala., and set forth clear indications as to when to give and when not to give vaccine treatment. They recall the hysteria and the resultant errors in judgment regarding the use of vaccine, which often lead to wastefulness in giving it to persons who do not need it. The harm which may follow as a result of numerous complications of vaccine treatment must also be considered.

They emphasize that the value of vaccine treatment as a life-saving measure is exaggerated. Of 48 persons who died of rabies, 23, or 48 per cent, were judged to have had prompt and adequate treatment. Ratcliffe,[168] in Indiana, found that 12 of 40 patients who died had received the Pasteur treatment and that the duration of the disease in the treated patients did not differ from that in the untreated ones. In 4 of 6 fatal cases studied by Leach and Johnson,[169] Pasteur treatment had been given early.

The Birmingham observers [167] point out the rarity of the disease in man as compared with its frequency among dogs (1 per cent); it is therefore not easily contracted. Nevertheless, because of its great danger, patients receiving bites and scratches from rabid animals should always be treated with vaccine, in spite of the hazard of vaccine paralysis or other serious complications of the treatment itself. The problem of the control of rabies, they state, appears to be one of home-owned pets and not particularly of unidentified stray dogs.

Health officers of Los Angeles [170] criticize the paper of Denison and Dowling as dangerous in overemphasizing the deficiencies in treatment

165. Gloyne, L.: Dog Bites and Rabies, Correspondence, J. A. M. A. **113**:1752 (Nov. 4) 1939.

166. Kellogg, W. H.: Treatment of Bites of Rabid Animals, Correspondence, J. A. M. A. **114**:910 (March 9) 1940.

167. Denison, G. A., and Dowling, J. D.: Rabies in Birmingham, Alabama: Human Mortality as Affected by Antirabies Treatments, J. A. M. A. **113**:390-395 (July 29) 1939.

168. Ratcliffe, A. W.: Rabies in Indiana: Survey 1926 to June 1938, with Analysis of Human Deaths, J. Indiana M. A. **32**:366-371 (July) 1939.

169. Leach, C. N., and Johnson, H. N.: Human Rabies with Special Reference to Virus Distribution and Titer, Am. J. Trop. Med. **20**:335-340 (March) 1940.

170. Pomeroy, J. L., and Swartout, H. O.: Rabies, Correspondence, J. A. M. A. **113**:1898-1899 (Nov. 18) 1939.

and object to their statistical analysis. In defense Denison and Dowling [171] reply, with justification, I believe, that any reflection on the efficacy of antirabies vaccine renders the control of dogs even more important.

Webster [172] reviewed the literature concerning antirabies immunization and, contrary to expectations, found a surprisingly meager amount of evidence supporting the use of vaccine. The published results are generally inconsistent and nonquantitative. Pasteur's tests on the immunization of dogs, for example, have not been confirmed. Over a period of fifty years only 1 of 10 investigators, Fermi, obtained definite protection *after* virus had been introduced, and the amount of vaccine given his animals was at least 25 per cent of the body weight. Even Fermi's work is unconfirmed. The results of other experiments were slightly more hopeful but only when vaccine was given *before* infection. The results of the experiments in general are irregular and show not only meager immunizing power in vaccines but little superiority of one preparation or procedure over another. Webster [173] describes a reliable method whereby the potency of antirabies virus may be tested in mice.

Kelser [174] in a review of the subject points out that rabies develops in only about 25 per cent of persons bitten by rabid dogs. On this basis any form of preventive measure used may be credited with 75 per cent efficacy, irrespective of whether or not its effect was specific. In spite of this fact it can be concluded from published statistics that vaccine, even of low potency, will prevent the disease in a certain proportion of the 25 per cent of cases just referred to.

It is clear that the problem of the prevention and treatment of rabies is far from being settled and is in need of further investigation. Far too much reliance is placed on the life-saving power of antirabies vaccine, partly because of the favorable statistics shown in data published by the League of Nations; yet it should be used when definitely indicated. It is far better to control the disease at its source—namely, among dogs.

Interesting observations in Venezuela [175] show that a form of rabies causing paralysis in livestock may be transmitted by blood-sucking vampire bats. Bats themselves suffer no ill effects. According to Good-

171. Denison, G. A., and Dowling, J. D.: Rabies in Alabama, Correspondence, J. A. M. A. **114**:76-77 (Jan. 6) 1940.

172. Webster, L. T.: The Immunizing Potency of Antirabies Vaccines: A Critical Review, Am. J. Hyg. (Sect. B) **30**:113-134 (Nov.) 1939.

173. Webster, L. T.: A Mouse Test for Measuring the Immunizing Potency of Antirabies Vaccines, J. Exper. Med. **70**:87-106, 1939.

174. Kelser, R. A.: The Epidemiology and Prophylaxis of Rabies, Virus and Rickettsial Diseases, Cambridge, Mass., Harvard University Press, 1940, pp. 642-660.

175. Iturbi, J., and Gallo, P., abstracted, Science (supp.) **91**:12 (May 24) 1940.

pasture,[175a] Dawson modified a strain of rabies virus by passage through chick embryos, so that it caused only self-limited encephalitis in rabbits but left solid immunity to a heavy dose of "street" virus.

Smallpox Vaccine.—Donnally [176] compared the relative merits of calf lymph virus and the new culture vaccine virus of Rivers. Both types of vaccine evoke similar skin reactions in babies when injected intradermally. However, when immunity was tested by revaccination, 73 per cent of 34 infants vaccinated with calf lymph virus were immune as compared with only 5.5 per cent of 36 children vaccinated with culture virus lymph. It is uncertain, of course, whether immunity to revaccination is as satisfactory a test as immunity to spontaneous infection, but it is unfortunate that the culture virus is not more efficacious, since it has a number of advantages over calf lymph virus.

In the experience of Ellis and Boynton,[177] calf lymph virus gave a higher percentage of primary "takes" among university students than culture virus vaccine. Local and constitutional reactions were somewhat less with Goodpasture's vaccine than with calf lymph material, but River's vaccine frequently gave constitutional reactions when inoculated intracutaneously.

A comment in the *Public Health Reports* [178] emphasizes the necessity of rigid enforcement of vaccination as a preventive measure against smallpox. In New Jersey, where vaccination is common, with a population of 4,400,000, no smallpox has been reported in seven years; in seven western states where vaccination is loosely enforced, 12,000 cases were reported in the same period in a smaller population.

More evidence has been given that vaccinia represents a "degraded" virus of variola, a virus which has lost a specific antigen.[179] Its virulence for man is diminished, but a wider range of infectivity for different animal species is gained. Cross immunity between vaccinia and variola, though strong, is not completely reciprocal. Protection induced by vaccinia is complete against both viruses, but that of variola is complete

175a. Goodpasture, E. W.: Immunity to Virus Diseases, New England J. Med. **222**:901-910 (May 30) 1940.

176. Donnally, H. H.: Smallpox Vaccination of Infants: Revaccination After Two to Three Years in Children Primarily Vaccinated with Culture Virus (Rivers), Compared with Those Primarily Vaccinated with Calf Lymph Virus, J. A. M. A. **113**:1796-1800 (Nov. 11) 1939.

177. Ellis, R. V., and Boynton, R. E.: Smallpox Vaccination: Comparison of Vaccines and Technics, Pub. Health Rep. **54**:1012-1025 (June 9) 1939.

178. Why Smallpox? Pub. Health Rep. **54**:1091-1092 (June 23) 1939.

179. Horgan, E. S., and Haseeb, M. A.: Cross Immunity Experiments in Monkeys Between Variola, Alastrim and Vaccinia, J. Hyg. **39**:615-637 (Nov.) 1939.

only against itself and usually complete against vaccinia. Complete immunity is largely dependent on the intensity of the primary reaction.

Psittacosis.—Meyer and Eddie [180] have devised a complement fixation test which they claim is an invaluable aid in the early and late diagnosis of psittacosis.

FOOD POISONING

Botulism.—Watson [181] reports an outbreak of botulism in Seattle. Sixteen patients were studied. They were treated with botulinus antitoxin, and 5 died, a mortality rate of about 30 per cent. Watson holds that the use of antitoxin is imperative in all cases regardless of the duration of symptoms or of the length of the incubation period, a stand with which most physicians will agree, since treatment with antitoxin is the only specific therapy available. On the other hand, the number of cases reported is far too small for one to conclude with Watson that this treatment was responsible for the low mortality rate. One feels that much more knowledge of the problem is necessary. Studies similar to the ones of Abel and his associates on tetanus should be made to determine whether or not botulinus antitoxin can attack or neutralize toxin already absorbed. The paper contains detailed instructions as to the use of antitoxin, artificial respiration and other means of treatment.

A few studies have been made in this country on the subject. Recently Schneider and Fisk [182] were able to demonstrate the toxin in the blood in 1 fatal case and in extracts of the liver in 2 others. Toxin was present in one liver even though 10,000 units of antitoxin (A and B) had been given five hours before death. No toxin was found in the blood of 3 patients who recovered. The demonstration of the toxin is a valuable aid in diagnosis.

Toxemia from Salmonella.—Two localized outbreaks of food poisoning caused by "Salmonella newport" have been described. In 1 case [183] liver paste was probably contaminated during its preparation by unhygienic methods.

Another interesting study of an outbreak caused by Salmonella aertrycke was made in Kansas.[184] Contaminated food served in an

180. Meyer, K. F., and Eddie, B.: The Value of the Complement Fixation Test in the Diagnosis of Psittacosis, J. Infect. Dis. **65**:225-233 (Nov.-Dec.) 1939.

181. Watson, W. E.: Treatment of Botulism, Northwest Med. **38**:382-387 (Oct.) 1939.

182. Schneider, H. J., and Fisk, R.: Botulism: Demonstration of Toxin in Blood and Tissues, J. A. M. A. **113**:2299-2300 (Dec. 23) 1939.

183. Andrew, D. H.; Korff, F. A., and Ewing, C. L.: Two Related Outbreaks of Food Poisoning Attributed to a Salmonella Organism, J. A. M. A. **113**:2300-2302 (Dec. 23) 1939.

184. Brown, E. G.; Combs, G. R., and Wright, E.: Food-Borne Infection with Salmonella Aertrycke, J. A. M. A. **114**:642-644 (Feb. 24) 1940.

orphanage made 52 out of a group of 71 persons sick, some of them seriously, and 1 died. The source of the trouble was traced to pudding made with duck eggs. Duck eggs are especially liable to infection with Salmonella, since they are usually laid in wet places contaminated with feces, and Salmonella are known to be able to enter the egg through the intact shell. Moreover, the egg may harbor the bacteria from its earliest stage, probably as a result of infection of the oviduct during copulation. In the outbreak studied, S. aertrycke was recovered from the feces of 9 ducks on the premises, and the blood of 3 agglutinated these bacilli. Similar bacteria were also recovered from the pudding and from the feces of 17 patients. Whether the bacilli were habitually present in the ducks or were introduced into the flock by infected excrement from a caretaker who was sick with a similar disease a week earlier is unknown, but I should favor the former possibility. The caretaker also probably ate duck eggs.

RICKETTSIAL DISEASES

Topping and Dyer [185] isolated a strain of the rickettsias of Rocky Mountain spotted fever from a patient near Washington, D. C., which resembles in all respects the typical virulent so-called western type. The terms "eastern" and "western," therefore, are apparently no longer useful; it may be better to classify various strains on the basis of virulence or of behavior in inoculated guinea pigs.

Parker,[186] testing ticks incident to a survey of possible disease-carrying ticks in Texas, encountered two strains of an infectious agent pathogenic for guinea pigs. These strains caused fever, scrotal edema and reddening, splenomegaly and immunity to subsequent infection. They seem gradually to lose virulence during transfer from animal to animal, and can be maintained only by repeated passage of testicular washings. Although a degree of cross immunity with Rocky Mountain spotted fever, boutonneuse fever and endemic typhus fever is established, the temperature reaction to the newly discovered infection is shorter and lower than that to any of the infections just named. The rickettsia-like bodies which were found resembled those of Rocky Mountain spotted fever.

Cox [187] reports further experiments on the newly isolated Rickettsia diaporica, so named because it can be passed through a porcelain filter.

185. Topping, N. H., and Dyer, B. E.: A Highly Virulent Strain of Rocky Mountain Spotted Fever Virus Isolated in the Eastern United States, Pub. Health Rep. **55**:728-731 (April 26) 1940.

186. Parker, R. R.: Observations on an Infectious Agent from Amblyomma Maculatum, Pub. Health Rep. **54**:1482-1484 (Aug. 11) 1939.

187. Cox, H. R.: Studies of a Filter-Passing Infectious Agent Isolated from Ticks, Pub. Health Rep. **54**:1822-1827 (Oct. 6) 1939.

Because of this property it should perhaps be classified as a new genus, differing from other rickettsias. Three more strains were collected in Wyoming and studied by Davis.[188]

Lewthwaite and Savoor[189] give a detailed description of tsutsugamushi disease and show that it is the same as "rural typhus," "scrub typhus" and "Sumatran mite fever." The latter terms are therefore redundant and should be abolished.

The engineering methods for the control of rats and murine typhus are described by Boston.[189a]

Rickettsial Vaccines.—In a short paper reviewing the development of rickettsial vaccines, Zinsser and his assistants[190] report a new technic for producing vaccine against the epidemic form of typhus on a large scale. Typhus rickettsias grown in eggs are transferred to minced chick tissue cultures for growth. Subcultures are subsequently spread on the surface of relatively large expanses of agar in modified Kolle flasks for growth and later harvesting. A team of 3 persons can make sufficient vaccine in a week for 300 immunizations.

A vaccine has been prepared by Cox and Bell[191] which protects guinea pigs from infection with the endemic (murine) form of typhus. Clinical trials are about to be made. They also report the preparation of a vaccine capable of protecting guinea pigs against epidemic typhus, but it is not so effective as that against the endemic variety.

Fitzpatrick[192] vaccinated 2 monkeys subcutaneously with formaldehydized "tissue culture" typhus rickettsia vaccine. Neither showed the Weil-Felix reaction, but both had low agglutinin titers for rickettsias after several weeks, and both were immune to inoculation with live typhus rickettsias. In contrast, typical typhus fever developed in an unvaccinated monkey, together with a Weil-Felix reaction titer of 1 : 640 and a rickettsia agglutination titer of 1 : 1,280. A vaccine of eastern

188. Davis, G. E.: Rickettsia Diaporica: Recovery of Three Strains from Dermacentor Andersoni Collected in Southeastern Wyoming; Their Identity with Montana Strain 1, Pub. Health Rep. **54**:2219-2227 (Dec. 15) 1939.

189. Lewthwaite, R., and Savoor, S. R.: Rickettsia Diseases of Malaya: Identity of Tsutsugamushi and Rural Typhus, Lancet **1**:255-259 (Feb. 10) 1940.

189a. Boston, R. J.: Public Health Engineering Phases of Murine Typhus Control, Am. J. Pub. Health **30**:619-626 (April) 1940.

190. Zinsser, H.; Plotz, H., and Enders, J.: Mass Production of Vaccine Against Typhus Fever and of the European Type, Science **91**:51-52 (Jan. 12) 1940.

191. Cox, H. R., and Bell, E. J.: Epidemic and Endemic Typhus: Protective Value for Guinea Pigs of Vaccines Prepared from Infected Tissues of the Developing Chick Embryo, Pub. Health Rep. **55**:110-115 (Jan. 19) 1940.

192. Fitzpatrick, F. K.: Vaccination of Monkeys with Agar-Tissue Cultures of European Rickettsia, Proc. Soc. Exper. Biol. & Med. **42**:217-218 (Oct.) 1939; Vaccination Against Spotted Fever with Agar-Tissue Cultures, ibid. **42**:219-220 (Oct.) 1939.

type Rocky Mountain spotted fever prepared in the same manner protected guinea pigs against spotted fever.

After unsuccessful trials by others, Topping [193] was able to make an antiserum which protects a large majority of guinea pigs and monkeys against experimental infection with rickettsias of Rocky Mountain spotted fever. The serum was prepared by vaccinating rabbits first with formaldehydized vaccine and then with small but gradually increasing doses of active tick virus.

Malaria.—The Fondés [194] point out facts concerning malaria which most physicians not familiar with the disease seldom realize. The first is the importance of chronic malaria as comprising the majority of cases of malaria. It is easy enough to recognize the "classic" acute disease, with its regularly spaced paroxysms, splenomegaly and parasites in the blood, but the more widespread chronic form with its protean manifestations is easily mistaken for other diseases. Another point is that the malaria infection, like that of tuberculosis, syphilis, undulant fever, tularemia and others, is a tenacious one, persisting for years in spite of specific therapy. Specific therapy, it seems, merely renders the infection asymptomatic, somewhat, perhaps, in the way that the salicylates influence the symptoms but not the underlying infection in rheumatic fever. The authors refer to the recent important work of James and Tate, who demonstrated the existence of the vegetative cycle in the animal body, and of Taliaferro and Cannon, who showed that phagocytic activity renders the disease asymptomatic in spite of the fact that the parasites reproduce at the same rate. The authors rightly deplore the use of "standardized" procedures in treating the disease and outline a rational scheme of prevention and treatment.

The pessimistic or perhaps realistic views just stated are supported by the disillusioning conclusion of Scott.[195] He writes: " . . . malaria in warm climates is as bad, as rife, as prevalent as ever, and nearly as fatal as it was a quarter of a century ago," in spite of the amount of knowledge physicians have of the disease.

An excellent review of infectious mononucleosis was published by Bernstein [196] and of coccidiomycosis by Smith.[196a]

193. Topping, N. H.: Treatment of Infected Laboratory Animals with Immune Rabbit Serum, Pub. Health Rep. **55**:41-46 (Jan. 12) 1940.

194. Fondé, G. H., and Fondé, E. C.: Chronic Malaria: A Clinical Consideration, Arch. Int. Med. **64**:1156-1169 (Dec.) 1939.

195. Scott, H. H.: A History of Tropical Medicine Based on the Fitzpatrick Lectures Delivered Before the Royal College of Physicians of London, 1937-1938, Baltimore, William Wood & Company, 1939.

196. Bernstein, A.: Infectious Mononucleosis, Medicine **19**:85-159 (Feb.) 1940.

196a. Smith, C. E.: Epidemiology of Acute Coccidiomycosis with Erythema Nodosum ("San Joaquin" or "Valley Fever"), Am. J. Pub. Health **30**:600-611 (April) 1940.

UNUSUAL AND RARE DISEASES

Leptospirosis.—From studies carried on chiefly in Europe, leptospirosis seems to be far more common and widespread than is at present believed. A disease or group of diseases called mud fever, swamp fever, field fever or harvest fever is often seen in such widely separated places as Germany, Russia, Italy,[197] Japan and Sumatra. Hundreds of harvesters had field fever one summer in Bavaria.[198] The disease in some places is caused by a spirochete called Leptospira grippotyphosa, and in others by Leptospira hebdomidis or Leptospira canicola, each of which is indistinguishable morphologically from the Leptospira icterohaemorrhagiae of Weil's disease. Rimpau [199] and others regard the infections as similar to Weil's disease, or the nonicteric form of it, since jaundice is present in less than 2 per cent of patients as compared with about 50 per cent in Weil's disease. It is my own feeling that jaundice is present in far less than 50 per cent of the cases if all mild cases of Weil's disease are included in the statistics. Because of the sudden onset, with high fever, conjunctival injection, severe headache, dizziness and aching of the limbs, mild attacks of leptospirosis without jaundice are often mistaken for influenza. The mortality from the other leptospiroses seems to be lower than that from Weil's disease. Joerdens [198] reports favorable results from treatment with specific immune serum. The best recent review of the subject is by Walch-Sorgdrager,[200] who also discusses prophylaxis with specific vaccines.

The close relationship of the micro-organisms causing mud, field or harvest fever to L. icterohaemorrhagiae and their serologic differences from this Leptospira are shown in studies by Karakašević.[201] A strain of leptospiras of rice field fever, according to Babudieri,[201a] was less virulent for guinea pigs than L. icterohaemorrhagiae and caused only multiple punctate hemorrhages in the lungs. The strain he studied was identical with Leptospira bataviae from Java, where the disease, as in Italy, occurs in rice harvesters.

The fact that jaundice is not a regular feature of Weil's disease may account for the probability that many cases are unrecognized in the

197. Mino, P.: Ueber Leptospirosen bei den Arbeitern der Reisfelder Oberitaliens, Ztschr. f. Immunitätsforsch. u. exper. Therap. **96**:466-520 (Oct. 2) 1939.

198. Joerdens, G.: Beitrag zur Klinik und specifischen Serumtherapie des Feldfiebers, München. med. Wchnschr. **85**:1979-1981 (Dec. 23) 1938.

199. Rimpau, W.: Weiteres zur Epidemiologie des Feldfiebers in Südbayern, München. med. Wchnschr. **85**:1977-1979 (Dec. 23) 1938.

200. Walch-Sorgdrager, B.: Leptospiroses, Bull. Health Organ. League of Nations **8**:143-386, 1938.

201. Karakašević, B.: Serologische Untersuchungen über die Spirochäte des Feldfiebers ("Spirochaeta grippo-typhosa"), Ztschr. f. Immunitätsforsch. u. exper. Therap. **96**:427-439 (Oct. 2) 1939.

201a. Babudieri, B.: R. C. Ist. san. pubbl., December 1939, p. 755.

United States. Since 1922 only 23 cases have been reported in American literature, in contrast with 248 in the British Isles [202] and 21 in Norway [203] since 1936. Many cases in this country are recognized but not reported. Havens and his associates [204] report the first instance in the United States of a small outbreak of Weil's disease in bathers. This occurred among 7 young men and was caused by swimming in a contaminated pool. The vicinity of the pool was infested with rats, the probable source of the infection. Two of the patients were severely ill; 1 of these died; the rest had mild attacks which ordinarily would not be diagnosed as Weil's disease.

Reticuloendothelial Cytomycosis (Histoplasmosis of Darling).—Several more cases of cytomycosis or histoplasmosis observed in the United States were reported from Washington, D. C.,[205] Richmond, Va.,[206] and Michigan.[207] As with many other supposedly rare diseases, it is probable that the disease occurs more commonly but is misdiagnosed. One case [205] was that of a girl whose illness began at 6 months of age, shortly after cow's milk was first used in feeding her. The disease lasted six months and was characterized by drowsiness, diarrhea and constipation, hepatomegaly, splenomegaly, fever and leukopenia. Parasitic bodies resembling Leishmania were found in large endothelial cells of the skin, liver, spleen, pancreas, intestine, lymph nodes, adrenal and bone marrow. The organism was first thought to belong to Leishmania, but others believe it to be one of the fungi imperfecti. Its true position is uncertain.

De Monbreun [208] found Histoplasma capsulatum the cause of the disease in the tissues of a dog, which is the first time the micro-organism has been discovered outside of man. He suggests that the dog may be the natural host of the disease, which may be spread to man by way

202. Alston, J. M.: Leptospirosis in the British Isles, abstracted, Report of the Proceedings of the Third International Congress for Microbiology, New York, Sept. 2-9, 1939, New York, The Congress, 1940, p. 638.

203. Thjötta, T., and Borgen, L.: Leptospira Infection in Norway, abstracted, Report of the Proceedings of the Third International Congress for Microbiology, New York, Sept. 2-9, 1939, New York, The Congress, 1940, p. 639.

204. Havens, W. P.; Bucher, C. J., and Reimann, H. A.: Leptospirosis: A Public Health Hazard; Report of a Small Outbreak in Bathers, J. A. M. A., to be published.

205. Shaffer, F. J.; Shaul, J. F., and Mitchell, R. H.: Histoplasmosis of Darling, J. A. M. A. **113**:484-488 (Aug 5) 1939.

206. Reid, J. D.; Scherer, J. H., and Irving, H.: Systematic Histoplasmosis in the United States, Science **91**:264 (March 15) 1940.

207. Humphrey, A. A.: Reticuloendothelial Cytomycosis (Histoplasmosis of Darling), Arch. Int. Med. **65**:902-918 (May) 1940.

208. De Monbreun, W. A.: The Dog as a Natural Host for Histoplasma Capsulatus, Am. J. Trop. Med. **19**:565-582 (Nov.) 1939.

of excreta. By an unusual coincidence, Chinese investigators in Peiping, China,[209] also decided that dogs were an important factor in the spread of canine leishmaniasis. Sandflies could be infected by feeding on dogs with cutaneous lesions. It is as yet uncertain whether canine and human leishmaniasis are identical, but dogs could be infected with material from human patients; furthermore, human kala-azar and canine leishmaniasis have been found in the same household.

The similarity of the conclusions reached by investigators in the United States and in China seems to me to favor the view that the micro-organisms of histoplasmosis belong in the group of Leishmania and not in that of the funguses. Clinically, the course of the disease is much more like that found in leishmaniasis than in fungous infections, yet De Monbreun and others have demonstrated the formation of mycelia in cultural studies and have transferred the disease to monkeys. Humphrey [207] believes the micro-organism to be unquestionably a fungus. I doubt that increased facilities for transportation accounts for the spread of the disease and the increasing number of recognized cases, as Humphrey suggests.

Yuan and his associates [210] feel that the development of kala-azar in young infants chiefly in the early summer months, at the time when sandflies are most prevalent, suggests that these insects may be important transmitters of the disease.

Toxoplasmosis.—Wolf, Cowen and Paige [211] report the fifth human case of granulomatous encephalomyelitis caused by a protozoon, Toxoplasma. The disease affects young infants and gives evidence of generalized involvement of the nervous system with miliary granulomas. There may be ophthalmoscopically identifiable lesions in the ocular fundi. In a later paper [212] they report the transfer of the infection to rabbits and mice. The morphologic aspects of the organisms in the human and in the animal lesions were identical. They suggest Toxo-

209. Feng, L. C.; Chung, H. L., and Hoeppli, R.: Canine Leishmaniasis with Skin Lesions Observed in Peiping, Chinese M. J. **55**:371-378 (April) 1939. Ho, E. A.: A Note on the Coincidence of Human Kala-Azar and Canine Leishmaniasis with Cutaneous Lesions in a Household, ibid. **55**:566-567 (June) 1939. Feng, L. C., and Chung, H. L.: The Development of Leishmania in Chinese Sandflies Fed on Dogs with Canine Leishmaniasis, ibid. **56**:35-46 (July) 1939.

210. Yuan, I. C.; Chu, F. T., and Lee, C. V.: Seasonal Incidence of Kala-Azar in Infants and Its Significance in Relation to the Transmission Problem of the Disease, Chinese M. J. **56**:241-264 (Sept.) 1939.

211. Wolf, A.; Cowen, D., and Paige, B. H.: Toxoplasmic Encephalomyelitis: A New Case of Granulomatous Encephalomyelitis Due to a Protozoon, Am. J. Path. **15**:657-694 (Nov.) 1939.

212. Wolf, A.; Cowen, D., and Paige, B. H.: Toxoplasmic Encephalomyelitis: IV. Experimental Transmission of the Infection to Animals from a Human Infant, J. Exper. Med. **71**:187-214 (Feb.) 1940.

plasma hominis as its name. Pinkerton and Weinman,[212a] after giving a historical review of the subject, report the first authentic case of toxoplasmosis in an adult and methods for the diagnosis and identification of the organism.

Miscellaneous.—Several unusual cases of endocarditis were studied. In one,[213] endocarditis occurred in a patient with erysipeloid. Erysipeloid in itself is an interesting disease, caused by Erysipelothrix rhusiopathiae and is most commonly found among fishermen and workers in abattoirs. It is known to the laity as "fish poisoning." The etiologic agent causes a similar disease, swine erysipelas (*Schweinerotlauf*), with endocarditis, in animals. In the other cases the endocarditis was caused by peculiar gram-negative cocci.[214]

A rare case[215] of abscess of the liver caused by Friedländer's bacilli and a case[216] of peritonitis caused by Coccidioides immitis were observed. Two cases of meningitis with recovery, caused by Micrococcus tetragenus, are reported.[217]

In the past few years several remarkable examples of excellent observation and association of facts have clarified the knowledge concerning important diseases involving both man and animals. For example, Alice Evans recognized and proved the relationship and identity of the microbes of Bang's disease of cattle and human brucellosis. In a similar manner, Francis in 1919 showed that deer fly fever and a plaguelike disease of rodents were both caused by Pasteurella tularensis and gave the disease its name, tularemia.

Recently more mystery and confusion have been cleared up. A relationship has been discovered in the cause of four diseases heretofore unassociated with one another, namely, (*a*) a form of rat bite fever, (*b*) Haverhill fever, (*c*) a cattle disease, pleuropneumonia, and (*d*) a disease of rats studied by Woglom. A number of years ago several

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212a. Pinkerton, H., and Weinman, D.: Toxoplasma Infection in Man, Arch. Path. **30**:374-392 (July) 1940.

213. Russell, W. D., and Lamb, M. E.: Erysipelothrix Endocarditis: A Complication of Erysipeloid; Report of a Case with Necropsy, J. A. M. A. **114**:1045-1050 (March 23) 1940.

214. Shiling, M. S.: Bacteriology of Endocarditis, with Report of Two Unusual Cases, Ann. Int. Med. **13**:476-486 (Sept.) 1939.

215. Boettiger, C.; Weinstein, M., and Werne, J.: Primary Suppuration of Liver Due to Friedländer's Bacillus, J. A. M. A. **114**:1050-1055 (March 23) 1940.

216. Ruddock, J. C., and Hope, R. B.: Coccidioidal Peritonitis: Diagnosis by Peritoneoscopy, J. A. M. A. **113**:2054-2055 (Dec. 2) 1939.

217. McGowan, T. S., and Kisner, P.: A Review of Meningitis Due to Micrococcus Tetragenus, Arch. Int. Med. **64**:15-25 (July) 1939. Criscitiello, M.: Meningitis Due to Micrococcus Tetragenus: Report of a Case with Recovery Following Treatment with Sulfanilamide, New England J. Med. **221**:383-385 (Sept. 7) 1939.

observers, notably Schottmüller (1914) and Blake (1916), reported an unusual form of disease following the bite of a rat. The causative organism seemed to be Streptothrix muris ratti or Streptobacillus moniliformis. For many years these observers were suspected of having made the mistake of isolating a saprophyte instead of the actual etiologic agent in a case of rat bite fever, or sodoku, as caused by the better known Spirillum minus (Treponema morsus muris), a disease which can be cured with arsphenamine. Subsequent facts have proved that they were correct. Sodoku, or rat bite fever, is indeed caused by a spirillum, but the disease they studied, though it followed a rat bite, was caused by a different organism. The next important observation was made in 1926, when a localized epidemic of an unusual febrile disease occurred in Haverhill, Mass. The syndrome described by Place, Sutton and Willner was called Haverhill fever. It was supposedly caused by a highly pleomorphic filamentous gram-negative organism, called Haverhillia multiformis. A similar disease had been reported by Levaditi in 1925. In neither of these instances were rats suspected as the source of infection.

The third link in the chain of information came with the realization that S. moniliformis and H. multiformis were similar, if not identical, micro-organisms. The subject is summarized by Farrell, Lordi and Vogel [218] and others.[218a]

Perhaps the most intriguing of all discoveries in this field dates from Klieneberger's work after 1935. She observed that curious colonies composed of delicate bodies, which she called L organisms, commonly occurred among typical colonies of S. moniliformis. These new forms she regarded as unrelated symbionts. The L forms resembled very closely the minute organism associated with pleuropneumonia bovis, which is a member of a group of bacteria pathogenic for animals. In their properties these micro-organisms differ in a number of ways from commonly known bacteria and often pass through porcelain filters.

Subsequent to these studies, Dienes [219] and Dawson [220] modified the interpretation of Klieneberger and showed that the pleuropneumonia-like bacteria were not unrelated symbionts but actually a variant of

218. Farrell, E.; Lordi, G. H., and Vogel, J.: Haverhill Fever: Report of a Case with Review of Literature, Arch. Int. Med. **64**:1-14 (July) 1939.

218a. Albritten, F. F.; Sheely, R. F., and Jeffers, W. A.: Haverhillia Multiformis Septicemia: Its Etiologic and Clinical Relationship to Haverhill and Rat-Bite Fevers, J. A. M. A. **114**:2360-2363 (June 15) 1940.

219. Dienes, L.: L Organisms of Klieneberger and Streptobacillus Moniliformis, J. Infect. Dis. **65**:24-42 (July-Aug.) 1939. Dienes, L., and Sullivan, E. R.: Morphology and Nature of Pleuropneumonia-like Microorganisms, Proc. Soc. Exper. Biol. & Med. **41**:424-426 (June) 1939.

220. Dawson, M. H., and Hobby, G. L.: Rat-Bite Fever, Tr. A. Am. Physicians **54**:329-332, 1939.

S. moniliformis. Transformation of one form to the other was repeatedly noted. Thus there is added more important information concerning transformations of bacterial type, the occurrence of which I noted several years ago among strains of M. tetragenus.

Pleuropneumonia-like organisms were for a brief period suspected of having some etiologic relations with rheumatic fever,[221] but subsequent work has shown otherwise. The micro-organisms supposedly isolated from patients with rheumatic fever most probably were present in the lungs of the inoculated mice used in the experiments.[222] In mice and rats inoculated intranasally with cultures pneumonia develops, and occasionally pleuritis.[223] In my review of 1938,[224] Woglom's "pyogenic virus" of rats was mentioned. This unusual agent, whose nature was undetermined at the time, was recently identified by Klieneberger[225] as a pleuropneumonia-like organism. Similar micro-organisms were found in the genitalia of about one third of a small number of women whose secretions were submitted for the detection of gonococci.[225a] Whether the pleuropneumonia-like organisms as identified by morphologic criteria were potentially pathogenic was not determined.

Sulfanilamide and neoarsphenamine had no influence in curing mice of experimental infection with S. moniliformis, but a single injection of gold sodium thiomalate (myochrysine) was sufficient to protect them from fatal doses.[226]

Other interesting observations on microbic dissociation were made by Dienes,[227] concerning a culture of colon bacilli. Tiny colonies were seen

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221. Swift, H. F., and Brown, T. M.: Attempts to Cultivate Pleuropneumonia-like Microorganisms from Rheumatic Exudates, abstracted, Reports of the Proceedings of the Third International Congress for Microbiology, New York, Sept. 2-9, 1939, New York, The Congress, 1940, p. 183. Sabin, A. B.: Filtrable Mesenchymotropic Microorganisms Producing Experimental Polyarthritis and Choreiform Syndromes in Mice, ibid., p. 182.

222. Sabin, A. B.: Mice as Carriers of Pathogenic Pleuropneumonia-like Microorganisms, Science **90**:18-19 (July 7) 1939.

223. Dienes, L., and Sullivan, E. R.: Pneumonia in White Mice Produced by a Pleuro-Pneumonia-like Microorganism, Proc. Soc. Exper. Biol. & Med. **41**:620-622 (June) 1939.

224. Reimann, H. A.: Infectious Diseases, Arch. Int. Med. **62**:305-352 (Aug.) 1938.

225. Klieneberger, E.: Studies on Pleuro-Pneumonia-like Microorganisms; L4 Organism as Cause of Woglom's "Pyogenic Virus," J. Hyg. **39**:260-265 (May) 1939.

225a. Dienes, L.: Cultivation of Pleuropneumonia-like Organisms from Female Genital Organs, Proc. Soc. Exper. Biol. & Med. **44**:468-469 (June) 1940.

226. Heilman, F. R.: Chemotherapy in Experimental Infections Caused by Streptobacillus Moniliformis, Science **91**:366-367 (April 12) 1940.

227. Dienes, L.: A Peculiar Reproductive Process in Colon Bacillus Cultures, Proc. Soc. Exper. Biol. & Med. **42**:773-778 (Dec.) 1939.

to be composed of long wavy filaments, showing all grades of transition into large fusiform or round bodies. In 1 instance, out of many thousand observations, the contents of the large bodies and of the filaments seemed to be composed of masses of bacilli, morphologically similar to normal colon bacilli. They may represent a special form of transformation rarely encountered in bacteriologic studies.

Further interesting work on microbic dissociation was done by Randall,[228] who studied the mucoid, translucent and rough culture phases of a strain of Friedländer's bacillus. The smooth translucent forms resembled the colonies of Escherichia coli, and because of the production of acid and gas in certain mediums, they could not be distinguished from the Citrobacter group of bacteria. The serologic reactions of the original types and of the variants derived therefrom revealed strict type specificity and in some cases individual specificity with the type. These results are so similar to the ones I reported for M. tetragenus several years ago that a parallelism is suggested. The resemblances between apparently unrelated bacteria, such as the Klebsiella and the Citrobacter group, as just told, calls to mind other recently discovered similarities between apparently unrelated bacteria, all of which involve microbic dissociation, namely, the resemblance of certain R pneumococci to Streptococcus viridans and of M. tetragenus to Staphylococcus and the interesting relationship of S. moniliformis to the pleuropneumonia-like organisms.

228. Randall, W. A.: Colony and Antigenic Variation in Klebsiella Pneumoniae Types A, B and C, J. Bact. **38**:461-471 (Oct.) 1939.

News and Comment

Mississippi Valley Medical Society Contest.—Dr. John F. Casey, visiting physician, St. Elizabeth's Hospital, Boston, won the third annual Essay Contest of the Mississippi Valley Medical Society "for the best unpublished essay on a subject of practical and applicable value to the general practitioner of medicine" and will receive a cash prize of $100, a gold medal, a certificate award and an invitation to present his essay at the annual meeting of the Mississippi Valley Medical Society. Dr. F. Stanley Morest, Kansas City, Mo., received the second certificate of merit and Dr. Charles W. Pavey, Columbus, Ohio, the third. Dr. Casey will address the Mississippi Valley Medical Society on the subject of his winning essay, "A Study of the Use of Sulfapyridine and Sulfathiazole in Pneumonia with Particular Reference to the Treatment of Pneumonia by the General Practitioner," at Rock Island, Ill., on Sept. 26, 1940. Dr. Casey's paper, and probably those of Drs. Morest and Pavey, will be published in the January 1941 issue of the *Mississippi Valley Medical Journal*, the society's official publication.

Mississippi Valley Medical Society.—The sixth annual meeting of the Mississippi Valley Medical Society will be held at the Hotel Fort Armstrong, Rock Island, Ill., Sept. 25 to 27, 1940. There will be numerous lectures, demonstrations, round table discussions and short instructional courses. At the annual banquet on September 26 Dr. N. B. Van Etten, New York, President of the American Medical Association, and the presidents of the Illinois State Medical Society, the Missouri State Medical Association and the Iowa State Medical Society will be speakers.

The complete program appears in the September issue of the *Mississippi Valley Medical Journal*, and further information may be secured from the secretary, Harold Swanberg, M.D., W. C. U. Building, Quincy, Ill.

American Congress of Physical Therapy.—The nineteenth annual scientific and clinical session of the American Congress of Physical Therapy will be held Sept. 2 to 6, 1940, at the Hotel Statler, Cleveland. The mornings will be devoted to an instructional seminar, and the scientific program will be presented in the afternoons and evenings. The complete course consists of twelve lectures from a list of forty-eight on diversified subjects. The scientific program itself consists of papers, demonstrations and motion pictures covering every branch of physical therapy. There will be a separate scientific program covering subjects pertaining to the eye, ear, nose and throat.

Further information may be obtained by writing directly to the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago.

Bicentennial Conference at the University of Pennsylvania.—A bicentennial conference will be held by the University of Pennsylvania in Philadelphia, September 16 to 20. The conference will form part of a bicentennial week program commemorating the two hundredth anniversary of the origin of the University of Pennsylvania. The speakers will include more than 200 American and European scholars and leaders in various fields of science and thought.

Six general fields—fine arts, humanities, medical sciences, natural sciences, social sciences and religion—will be covered by the conference, during the course of which there will be eighteen general sessions and fifty-nine symposiums.

Membership in the five day conference will carry with it the privilege of attending the general sessions and symposiums and will be open without charge, on application and within the limit of accommodations, to those interested in the program.

Applications for membership may be addressed to the Registrar of the Bicentennial Conference, University of Pennsylvania, Philadelphia.

Book Reviews

Textbook of Pathology: A Correlation of Clinical Observations and Pathological Findings. By Charles W. Duval, M.D., and Herbert J. Schattenberg, M.D. Price, $8.50. Pp. 681, with illustrations. New York: D. Appleton-Century Company, 1938.

The appearance of a new book on a subject about which there already exists a not inconsiderable number of textbooks requires a certain amount of explanation. The authors have given this in their preface. It is their purpose, they say, to stress "the relationship between pathologic physiology and altered tissue changes or morbid anatomy." The description of the disturbance in physiologic processes which results from a pathologic process somewhere in the body is a feature which has been completely neglected in most textbooks of pathology. The physician obtains but little help from most of the books on pathology when he wants to correlate the symptom complex or the symptoms with the underlying morbid anatomy. Duval and Schattenberg make a very excellent attempt to rectify this deficiency. In practically every section of the book, following the gross and microscopic appearance of a diseased organ, there is a subsection which is captioned "Correlation." Under this subheading there is a more or less detailed explanation for the symptoms which arise during the course of the disease, with particular emphasis on the reason for the patient's death. This subsection does much to enhance the value of the book to the physician who is not an actively practicing pathologist and who is more interested in the *why* of death than in *what* causes it.

The authors have divided the book into some twenty chapters. The first chapter has to do with exudative, proliferative and degenerative processes in disease. The next chapter is concerned with the etiology of disease and the reactions of fever, immunity, shock and anaphylaxis. After these two more or less introductory chapters the various systems of the body are taken up, in succeeding chapters, in considerable detail. Not only are the diseases dependent on pathologic changes in an organ discussed but also such disorders as the deficiency diseases, diseases of the blood and neoplasia are considered. The last chapter, of some thirty pages, has to do with the autopsy.

Succeeding each chapter is a list of references to articles which have been written on the subject in the English language. Duval and Schattenberg say that the average medical student has such a poor reading knowledge of foreign languages that it is difficult for him to make use of literature in those languages. Unfortunately, the references are neither numbered nor in alphabetical order. This makes for some confusion; when one wishes to refer to an article by Whipple, for example, it is necessary to read down the list of references until one finds the name, whereas if the names were listed alphabetically a glance at the end of the list would show the reference.

One of the very commendable features of the book is the minimization of histopathology. After all, the medical student or the practicing physician rarely has the ability to make exact histologic diagnoses, nor does the occasion particularly call for such ability. It seems regrettable that this thought was not carried out in the section on neoplasia. This is a very long chapter, of some 105 pages, and considerable detail is given concerning tumors which are extremely rare and which might confound even the skilled pathologist. However, many of these pages are of illustrations, which are very helpful.

Of course certain statements made in the book are tinctured somewhat by the personal reactions of the authors—for example, that the etiologic factor in pellagra is a virus. Furthermore, so rapid have been the advances in the study of the deficiency diseases and the endocrine disorders that one cannot blame the contributors if some of the statements they make have already become outdated.

Another criticism has to do with the amount of space that is given to leprosy. In view of the interest of the senior author in this condition the reason for the overattention to it is obvious. However, it does seem that a disease which attacks so few people in this country (at most not more than 50 or 60 persons yearly) hardly warrants three colored plates, eight figures and eleven pages of text.

Such criticisms are minor. Fundamentally the whole work is so excellent that the trivial objections are more than outweighed. Particularly to be praised is the very large number of excellent photomicrographs. The book can be recommended, without qualification, as a textbook, and it should be of particular value to the practitioner of medicine who wants to know the why and the wherefore of disease.

The Treatment of Rheumatism in General Practice. By W. S. C. Copeman, M.D., Physician in Charge of the Department of Chronic Rheumatic Diseases, West London Hospital. Price $4. Third edition. Pp. viii + 276. Baltimore: The Williams and Wilkins Company, 1939.

Just as it always is pleasant to meet an attractive person, so it is equally pleasant to be introduced to an attractive book. "The Treatment of Rheumatism in General Practice" falls in this category.

The first edition was published in 1933. It was two hundred and fifteen pages long, it sold for $3.25 in this country and it was highly spoken of by the critical minded. Our colleague, *The Journal of the American Medical Association* (**102**: 397-398 [Feb. 3] 1934), gave it a very favorable review. It was pointed out that there were a few minor faults in the book, particularly omission of any bibliographic references to the eighty authors mentioned, lack of discussion of gout, the disease so regularly mistaken by American physicians for rheumatic fever or chronic arthritis, and little description of the methods available for desensitization and immunization in arthritis. But, on the whole, *The Journal* liked the book and considered it a practical small volume, distinctly useful to any one dealing with the therapy of arthritis.

The *British Medical Journal* (**2**:607-608 [Sept. 30] 1933) also praised the first edition and recommended it highly. This journal stated that the viewpoint of the author seemed logical and that he gave a carefully considered verdict, formed largely in the light of actual experience, on therapeutic values in rheumatism. It was noted that there were a few literary inelegances which might well be deleted in future editions.

British doctors, too, evidently appreciated the book, for a second edition was published in 1935. This was thirteen pages longer than the first edition and contained various corrections and improvements, including a discussion of gold salt therapy in rheumatism and remarks on the use of bee venom, histamine and intravenous calcium. The reviews of this edition which appeared in the *British Medical Journal* (**2**:787 [Oct. 26] 1935) and in the *Lancet* (**2**:1280 [June 1] 1935) were complimentary. On our side of the Atlantic the second edition made only a few friends, for apparently we were slow to appreciate its basic soundness. The *American Journal of the Medical Sciences* (**190**:273 [Aug.] 1935) said, however, what all who became acquainted with the book must have felt: that here was a book which was bound to be useful to many a perplexed practitioner who had the good fortune to have it fall into his hands.

The third edition is a little grander than its predecessors—sixty-one pages longer than the first edition and 75 cents more expensive. It runs true to form and continues to give a clearly presented, readable description of the treatment of rheumatism. Evidently the author is willing to accept criticism, for now gout is well discussed, desensitization and immunization receive due consideration, each author who is mentioned receives proper bibliographic reference and all literary inelegance seems to have been disciplined. The result is worth while. As was said of each previous edition, in so many different ways, all doctors who deal with arthritic patients will enjoy this book and will find it worth knowing. It summarizes the modern treatment of rheumatism comprehensively and in a particularly readable fashion.

Rural Medicine. Edited by G. M. Mackenzie, M.D. Price, $3.50. Pp. XVII + 268, with 58 illustrative charts and tables. Springfield, Ill.: Charles C. Thomas, Publisher, 1939.

This is an interesting book. Members of the staff of the Mary Imogene Bassett Hospital in Cooperstown, N. Y., realized that there was but little systematically documented evidence describing what rural medicine amounted to in this country today, what its problems were or, if one knew what they were, how they should best be faced. Therefore, to make a start at finding out more than what was known of such matters, the staff last October organized a conference.

The conference must have been both enjoyable and stimulating. The topics discussed covered a wide range of subject matter. First were considered matters clinical. There were papers on: the demography of Otsego County, by Dr. J. V. DePorte, director of the Division of Vital Statistics of the New York State Department of Health; rural hospital morbidity in Otsego County, by Dr. E. L. Crosby, of the department of biostatistics in the School of Hygiene and Public Health at Johns Hopkins University; acute abdominal surgical conditions in a rural hospital, by Dr. M. A. McIver, of Cooperstown; traumatic emergencies in a rural hospital, by Dr. J. H. Powers, Cooperstown; heart disease in a rural community, by Dr. F. F. Harrison, Cooperstown, and vascular disease in a rural community, by Dr. David Kydd, Cooperstown.

Next, the health department and school health programs in rural areas were talked over. These topics were introduced by Dr. A. W. Freeman, of Johns Hopkins University; Dr. M. F. Murray, of Cooperstown, and Dr. Haven Emerson, of Columbia University.

Postgraduate medical education in rural areas received consideration. In this panel were papers by Dr. J. D. Bruce, of the University of Michigan, and Dr. J. B. Youmans, of Vanderbilt University. Finally, the economics of rural medicine was debated by such authorities as Dr. R. L. Wilbur, of Leland Stanford University; Mr. O. D. Young, of the General Electric Company; Dr. V. M. Hoge, of the Public Health Service; Dr. L. C. Warren, of the Otsego County Medical Society; Dr. C. C. McCoy, of Cooperstown; Dr. M. M. Davis, of New York, and Dr. R. G. Leland, of the American Medical Association.

All the papers which were presented were discussed freely. The book includes the papers read and the discussions which they promoted. There is a bibliography on the general subject of rural medicine, compiled by Dr. David Kydd.

Mr. Young, in closing the conference, epitomized satisfactorily the usefulness of such a meeting. He said, "It is out of meetings of this kind that interchanges of opinion can be obtained, and progress made so that rigidities melt as between different groups and different individuals." It is pleasant for any one interested to be able to have attended the conference, even vicariously, by studying its record.

Textbook of Medicine. By Various Authors. Edited by J. J. Conybeare, M.C., D.M. Oxon., F.R.C.P., Physician to Guy's Hospital, London. Price, $6.75. Pp. 1112. Fourth edition. Baltimore: The Williams and Wilkins Company, 1939.

This fourth edition of Conybeare's textbook of medicine has had enough revision to keep it well abreast of the times. The chief addition is to the neurologic section, where 100 pages on "psychological medicine" have been added. One questions seriously whether the pages devoted to disorders of the nervous system are not superfluous, not only in this text but in any textbook of medicine intended primarily for medical students. Certainly in most didactic courses in neurology the instructor will prescribe one of the recognized neurologic texts; and the brief material of the medical text, if read at all, will only confuse a subject not too clear in any case. The same may be said of the sections which all texts of medicine contain on diseases of the skin. These chapters seldom exceed a hundred pages and are practically uniformly neglected in the ordinary courses on dermatology. Surely any textbook would not suffer if the three to four hundred pages

devoted to nervous and cutaneous diseases were occupied by an expansion of the general medical material, which has had to be seriously abbreviated to keep the book portable.

Conybeare's text is good, however, and there is not enough difference between the nomenclature, materia medica and ideas in this volume and those in ordinary American medical usage to cause difficulty. Curiously, a discussion of sulfanilamide and sulfapyridine did not get included during the revision, although the use of protamine zinc insulin is taken up and so is the shock treatment of schizophrenia with insulin and metrazol. The reviewer objects, on the grounds that serious confusion may result, to the use of 1 gr. for gr. j, and of 1 grm. for 1 gram (or Gm.). Teaching students dosages is difficult enough when two systems are used; and tragedy will be prevented only when students learn to write and read apothecaries' and metric units in a distinctive manner. One of the functions of a textbook should be to act as a model for the students' actions. This is a minor but not a captious criticism; and the fault is one which can be easily corrected. The text appears to be adequate for its purpose and is remarkably clear and well written. The typography is pleasing because a large, clear type face is used.

Hypertension and Nephritis. By Arthur M. Fishberg, M.D. Fourth edition. Price, $7.50. Pp. 779, illustrated with 40 engravings and a colored plate. Philadelphia: Lea & Febiger, 1939.

One of the standard monographs used alike by students and graduate physicians is Fishberg's "Hypertension and Nephritis." Of the books devoted to one subject or several related subjects there probably has been no one of its kind that has been more frequently quoted and more generally used, and rightly so. The author has given, in so far as the kidney is concerned, a truly splendid description of renal disease and all its many expressions. In this reference book the inquiring mind may find an excellent account of the pathologic physiology of renal function, and in it may be discovered chapters on azotemia, albuminuria, edema, uremia and tests of renal function which are thoroughly complete. Arterial hypertension in nephritis is most adequately covered. The sections on the nephroses, acute and chronic glomerular nephritis and focal nephritis contain a well rounded description of their clinical and laboratory expressions.

The last few chapters of the book have to do with essential hypertension, its concept, pathogenesis, clinical picture, diagnosis, prognosis and treatment.

It has been five years since the book was last revised. Since that time much has been added to the knowledge of Bright's disease and hypertension. In the preface the author lists a long series of changes that have been made in this edition of his work. Space does not permit recounting these many changes. Suffice it to say that he has incorporated Goldblatt's important contribution on the production of hypertension; a new chapter on azotemia has been added; the surgical treatment of hypertension is discussed in detail; the nature and treatment of the toxemia of pregnancy are presented, and many other important advances have been added.

As with all of the publishers' books, the format of the volume is excellent, there are remarkably few typographic errors and the paper is an excellent grade, so that altogether the book will make a splendid addition to any medical library.